Summary of Inhalation Carcinogenicity Study

of 2,4-Pentanedione

in F344 Rats

March 2010

Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on March 26, 2010.

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

Summary of Inhalation Carcinogenicity Study of 2,4-Pentanedione in F344 Rats

Purpose, materials and methods

2,4-Pentanedione (CAS No. 123-54-6) is a colorless liquid with a boiling point of 139°C (746 mmHg). It is soluble in ethanol, acetone, and water.

The carcinogenicity and chronic toxicity of 2,4-pentanedione (greater than 99.9% pure) were examined by inhalation exposure using F344/DuCrlCrlj (Fischer) rats. Groups of test animals were exposed to 2,4-pentanedione vapors at target concentrations of 0 (clean air), 100, 200 or 400 ppm(v/v) for 6 hours/day, 5 days/week for 2 years (104 weeks). Each group of test animals consisted of either 50 male or 50 female rats. Both sexes were exposed to each concentration of 2,4-pentanedione vapor. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the 2,4-pentanedione used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. It was analyzed by gas chromatography before and after its use to affirm its stability. Stainless-steel inhalation exposure chambers (volume: 7.6m³) were used throughout the 2-year exposure period. 2,4-Pentanedione vapor-air mixtures were generated by bubbling clean air through 2,4-pentanedione liquid and the mixtures delivered to the inhalation exposure chambers. Air concentrations of the 2,4-pentanedione in the inhalation exposure chambers were monitored at 15 min intervals by gas chromatography. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. All animals, including those found dead or in a moribund state as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. Urinalysis was performed near the end of the exposure period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five µm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of 2,4-pentanedione induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by

(Study No.0675)

Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

No significant differences in survival rates and clinical signs were found between any of the groups exposed to 2,4-pentanedione and their respective controls. The body weights of the males exposed to 200 and 400 ppm 2,4-pentanedione and females exposed to 400 ppm 2,4pentanedione were suppressed relative to their respective controls throughout the 2-year exposure period. However, the difference in the body weights between 200 ppm-exposed males and their controls became smaller toward the end of the exposure period. The terminal body weights of the 400 ppm-exposed males and females were 90% and 88% of their respective controls. Food consumption was slightly decreased in males exposed to 200 and 400 ppm 2,4pentanedione and in females exposed to 400 ppm 2,4-pentanedione compared with their respective controls. Mean corpuscular hemoglobin concentration was significantly increased in males exposed to 200 ppm 2,4-pentanedione and above. Plasma levela of γ -glutamyl transpeptidase was significantly increased in males exposed to 400 ppm 2,4-pentanedione. Significantly decreased plasma levels of triglyceride and significantly increased plasma levels of urea nitrogen were observed in females exposed to 400 ppm 2,4-pentanedione. There were no 2,4-pentanedione related changes in urinalysis parameters or organ weights in any of 2,4pentanedione administered groups.

No significant increases in the incidence of neoplastic lesions were found in any of the 2,4pentanedione-exposed groups of either sex compared with their respective controls. Nonneoplastic lesions in the nasal cavity were significantly increased in both sexes at doses of 200 ppm 2,4-pentanedione and above: squamous metaplasia of the respiratory epithelium, inflammation, hyperplasia of the transitional epithelium, and atrophy of the olfactory epithelium. Using nasal lesions as endpoint markers, the no-observed-adverse-effect-level (NOAEL) of 2,4pentanedione, exposure by inhalation, was 100 ppm 2,4-pentanedione in both male and female rats.

Conclusions

There was no evidence for carcinogenicity of 2,4-pentanedione in male or female rats.

	ose (ppm)	0	100	200	400	Peto test	Cochran- Armitage test
Nu	mber of examined animals	50	50	50	50		
benign tumor							
skin/appendage	keratoacanthoma	4	2	2	1		
subcutis	fibroma	8	6	3	5		
lung	bronchiolar-alveolar adenoma	3	4	3	0		
liver	hepatocellular adenoma	0	4	0	1		
pancreas	islet cell adenoma	3	2	7	2		
pituitary	adenoma	13	5	16	6		
thyroid	C-cell adenoma	3	8	9	3		
adrenal	pheochromocytoma	2	4	2	4		
testis	interstitial cell tumor	44	46	40	42		
mammary gland	fibroadenoma	0	3	0	1		
malignant tumor							
spleen	mononuclear cell leukemia	4	3	2	1		
thyroid	C-cell carcinoma	3	1	1	1		
peritoneum	mesothelioma	3	2	0	3		

Incidences of selected neoplastic lesions of male rats in the 2-year inhalation carcinogenicity study of 2,4-pentanedione

Incidences of selected neoplastic lesions of female rats in the 2-year inhalation carcinogenicity study of 2,4-pentanedione

I	Dose (ppm)	0	100	200	400	Peto test	Cochran- Armitage test
N	umber of examined animals	50	50	50	50		
benign tumor							
pituitary	adenoma	21	18	19	15		
thyroid	C-cell adenoma	7	6	4	0 **		$\downarrow \downarrow$
adrenal	pheochromocytoma	0	1	3	2		
uterus	endometrial stromal polyp	13	3 **	12	7		
mammary gland	fibroadenoma	5	4	3	5		
malignant tumor							
spleen	mononuclear cell leukemia	2	7	0	1		

Significant difference

*:p≦0.05		** :p≦0.01		(Fisher test)
$\uparrow:p{\leq}0.05$	increase	$\uparrow \uparrow : p \leq 0.01$	increase	(Peto, Cochran-Armitage test)
\downarrow : p \leq 0.05	decrease	$\downarrow \downarrow : p \leq 0.01$	decrease	(Cochran-Armitage test)

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TABLE A

CONCENTRATIONS OF 2,4-PENTANEDIONE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

(Study No.0675)

CONCENTRATIONS OF 2,4-PENTANEDIONE IN THE INHALATION CHAMBER OF THE 2-YEAR INHALATION STUDY

Group Name	Concentration(ppm) Mean ± S.D.
Control	0.0 ± 0.0
100 ppm	100.8 ± 0.9
200 ppm	200.9 ± 1.4
$400~{ m ppm}$	400.7 ± 2.3

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TABLE D1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

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	C	Control		100 ppm	Ш		200 ррш	E		400 ppm	uzo	
	Av. Wt.	No. of	Av. Wt.	% of	No. of	Av. Wt.	% of	No. of	Av. Wt.	% of	No. of	
Week		Surviv.		cont.	Surviv.		cont.	Surviv.		cont.	Surviv.	
on Study	~	50>		<50>			<50>			<50>		
0	123 (50)	50/50	-	100	50/50		100	50/50	123 (50)	100	50/50	
I	153 (50)	50/50	152 (50)	66	50/50	150 (50)	98	50/50	143 (50)	93	50/50	
2	_	50/50	_	101	50/50		100	50/50	178 (50)	97	50/50	
с С	_	50/50	-	100	50/50		66	50/50		94	50/50	
4	_	50/50	_	66	50/50		86	50/50		92	50/50	
5	-	50/50	-	66	50/50		98	50/50		92	50/50	
9	-	50/50	_	66	50/50		67	50/50		16	50/50	
7	_	50/50		66	50/50		67	50/50		16	50/50	
8	_	50/50	_	100	50/50		67	50/50	267 (50)	91	50/50	
6	_	50/50	_	66	50/50		97	50/50		60	50/50	
10	_	50/50	-	66	50/50		96	50/50	-	60	50/50	
11	_	50/50		66	50/50		96	50/50	287 (50)	60	50/50	
12	_	50/50		66	50/50		96	50/50	-	60	50/50	
13		50/50		66	50/50		96	50/50		60	50/50	
14		50/50		66	50/50		96	50/50	-	60	50/50	
18		50/50		66	50/50		96	50/50		60	50/50	
22	370 (50)	50/50	364 (50)	98	50/50		96	50/50		60	50/50	
26		50/50		8 6	50/50		96	50/50		91	50/50	
30	_	50/50		98	50/50		96	50/50	354 (50)	90	50/50	
34	_	50/50		98	50/50		96	50/50		60	50/50	
38	-	50/50		67	50/50		96	50/50		60	50/50	
42	-	50/50		66	49/50	405 (50)	96	50/50		89	50/50	
46	-	50/50		8 6	49/50		96	50/50		89	50/50	
50		50/50		98	49/50		95	50/50		88	50/50	
54	-	50/50		98	49/50		95	49/50		88	50/50	
58		50/50		8 6	49/50		95	49/50		88	50/50	
62		50/50		98	49/50		95	49/50		88	50/50	
66		50/50		98	49/50		95	49/50		89	50/50	
20		49/50		98	49/50		94	49/50		89	50/50	
74	-	49/50		98	49/50	428 (49)	94	49/50		68	50/50	
78		49/50		98	49/50		94	49/50		88	49/50	
82		49/50		66	49/50		96	48/50		68	47/50	
86 2.2	449 (48)	48/50	442 (48)	98 0	48/50	430 (48)	96 96	48/50	402 (45)	06	45/50	
90 9	-	47/50		98 5	46/50	-	96	47/50		68	45/50	
94	-	45/50		67	44/50	-	94	46/50	_	88	45/50	
98	-	43/50	-	8 6	43/50	-	96	43/50	_	60	43/50	
102	-	43/50		100	40/50	406(41)	66	41/50	375 (42)	$\overline{16}$	42/50	
104	A16 (A1)	11/50	(01) 617	\$								

MEAN BODY WEIGHTS AND SURVIVAL

: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj]

STUDY NO. ANIMAL

(B10040)

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TABLE D2

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BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

MEAN BODY WEIGHTS AND SURVIVAL

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]

Av.Wt.:g

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

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TABLE D3

BODY WEIGHT CHANGES : MALE

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SEX : MALE Group Name	a in imba	Administration work												PAGE :	
	0				3		3		4		£.		9		
Control	123±	ى	153土	œ	184±	6	212±	10	235±	11	$252\pm$. II	268土	12	
100 ppm	123土	വ	$152\pm$	7	185±	œ	211±	6	232±	10	$250\pm$	10	265土	11	
200 ppm	$123\pm$	വ	150土	œ	$184\pm$	10	209土	10	230±	10*	$246\pm$	11*	$261\pm$	11**	
400 ppm	123土	വ	$143\pm$	6**	178±	**/	± 661	**	217土	6 **	231±	3 ##	$243\pm$	10**	
			2 												

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] UNIT : g REPORT TYPE : Al 104 SEX : MALE	i [F344/DuCr j.	-		BODY	BODY WEIGHT CHANGES ALL ANIMALS	CHANGES	(SUMMARY)							PAGE :	7
Group Name	Admini 7	Administration week 7	week 8		6		10		. 11		12		13		
Control	281±	12	294±	13	305±	14	314±	14	320±	14	328±	15	$334\pm$	15	
100 ppm	279±	12	293±	12	$303\pm$	13	311±	13	317土	14	$324\pm$	15	$330\pm$	15	
200 ppm	272±	12**	284±	13**	295土	13***	302±	14**	308±	15**	315±	15**	$321\pm$	15**	
400 ppm	$255 \pm$	11**	267±	12**	$276\pm$	12**	283±	13**	287土	13**	$294\pm$	13**	$302\pm$	13**	
										2					
Significant difference;	*:P≦0.05	0.05	★* : P ≦ 0.01	10			Test of Dunnett	unnett							

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REPORT TYPE : A1 104 SEX : MALE														P	
Group Name	Admini 14	Administration week 14	1 week 18		22		36		30		34		38		
Control	$339\pm$	15	355土 1	17	370±	18	383±	19	394±	19	404±	22	414±	23	
100 ррп	335±	16	350土 1	17	$364\pm$	22	375±	28	385±	33	395±	37	$403\pm$	41	
200 ppm	326±	15**	341土 1	16**	356±	17**	368±	18**	378±	18**	389±	19**	398±	21**	
400 ppm	305±	14**	$321\pm$	16**	334±	17**	347±	19**	$354\pm$	19**	$364\pm$	20**	371±	21**	
Significant difference ;	*:P≦0.05	0.05	t+: P ≦ 0.01				Test of Dunnett	innett							

REPORT TYPE : A1 104 SEX : MALE														PA	PAGE :
Group Name	Admini 42	Administration week 42	week46		20		54		58		62		66		
Control	422土	23	427±2	24	434土	8	440±	24	442±	24	447±	24	448±	23	
100 ррш	416±	19	$420\pm$ 1	19	$425\pm$	18	431±	18	435±	18	439±	19	441±	21	
200 ppm	405±	21**	409± 2	22 * *	411±	23**	418±	24**	419土	26**	423±	28**	4 25±	25**	
400 ppm	376±	21**	379± 2	21**	384±	22**	389±	22★	390土	23**	$395\pm$	24**	399 +	23**	
Significant difference;	*:P≦ 0.05		★* : P ≦ 0.01				Test of Dunnett	unnett							

SEX : MALE		•	-											PAGE
Group Name	70	Administration week 70	reek 74		82		82		86		06		94	
Control	$451\pm$	23	453±	22	452土	23	$449\pm$	26	449土	23	447土	26	$439\pm$	36
100 ppm	443±	23	$445\pm$	22	$445\pm$	22	443±	25	442 ±	23	439±	25	428±	35
200 ppm	426土	30**	428±	36**	427±	40**	430土	27**	430土	27**	430土	25**	414土	42**
400 ppm	400±	27**	$402\pm$	32**	$399\pm$	29***	398±	3244	$402\pm$	19**	400土	20**	387±	23**
Significant difference : *	* • • • • • • • • • • • • • • • • • • •						Test of Dumett	++					:	

	200 ppm 410± 36** 406± 46 406± 50	UNIT : g REPORT TYPE : A1 104 SEX : MALE PAGE : 6		102 412± 45 413± 45 406± 46 375± 16**	410± 18**	REPORT TYPE : Al 104 SEX : MALE Group Name Control 100 ppm 200 ppm 400 ppm
		Administration week 102 104 98 102 104 itrol $426\pm$ 30 $412\pm$ 45 $416\pm$ itrol $426\pm$ 30 $412\pm$ 45 $416\pm$ itrol $419\pm$ 44 $413\pm$ 45 $413\pm$ itrol $410\pm$ $36**$ $406\pm$ 46 $406\pm$				400 ppm
410± 36** 406± 46 406± 382± 18** 375± 16** 374±		Administration week 102 104 98 102 104 104 101 426± 30 412± 45 416±				100 ppm
419± 44 413± 45 413± 410± 36** 406± 46 406± 382± 18** 375± 16** 374±	419± 44 413± 45 413±	Administration week 98 102				Control
426± 30 412± 45 416± 419± 44 413± 45 413± 410± 36** 406± 46 406± 382± 18** 375± 16** 374±	426± 30 412± 45 416± 419± 44 413± 45 413±		104		Administration 98	íame

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TABLE D4

BODY WEIGHT CHANGES : FEMALE

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STUDY NO. : 0675	BODY WEIGHT CHANGES	CHT CH	IANGES
ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj]	ALL ANIMALS	SJ	
UNIT : g			
REPORT TYPE : AI 104			
SEX : FEMALE			
	•		

(SUMMARY)

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SEX : FEMALE														PAGE : 7
Group Name	Admini	Administration week	week	•						N 2000 10 10 10 10 10 10 10 10				
	0		1		2		ç		4		ۍ	· ·	9	
Control	+ 66	ŝ	113±	4	127±	ى ئ	$138\pm$	9	147±	9	$155\pm$	2	161±	2
LOO ppm	+66	ŝ	112±	ស	126±	ល	136±	ß	145土	ę	153±	Q	158±	2
200 ppm	7 66	en	112±	വ	127±	Q	136±	9	145±	2	152±	œ	$159\pm$	œ
400 ppm	7 66	ę	$107 \pm$	4**	123土	6 **	131±	5⊭≭	139土	6 **	146土	6**	153±	6**
Significant difference ; *: P ≦ 0.05	* : P ≦0		** : P ≦ 0.01	1			Test of Dunnett	mett						

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KETORI TITE - AL 104 SEX : FEMALE			-											PAGE :	
uroup Name	L STUTEDV	7	week 8		6		10		11		12	,	13		
Control	166±	8	171±	8	$175\pm$	6	179土	10	182±	6	$186\pm$	10	188土	10	
100 ррш	164±	7	170±	8	$172\pm$	œ	177±	8	180±	8	183±	8	185土	ø	
. mdd 200	$163\pm$	6	168±	6	173±	10	$177\pm$	10	$179\pm$	6	182±	10*	183±	*6	
400 ppm	157±	7**	$162\pm$	8**	166±	8**	170±	**8 8	172±	8**	175±	8**	177±	8**	

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ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : FBMALE	j[F344/DuCr j]			ALL A	STEWIN	TINNER TRACT	TUTUTU							PAGE	6
Group Name	Administ 14	Administration week14	18		22		26		30		34		38		
Control	191 ± 10		197±	11	201±	12	208土	11	$211\pm$	12	218±	12	$223\pm$	13	
100 ppm	187± 5	9 1	193±	10	198±	11	204土	12	209土	12	217土	13	$221\pm$	13	
200 ppm	185± 10	10* 1	191±	11*	197±	11	202±	12*	206±	11	$213\pm$	12	217±	13*	
400 ppm	178± 9	9** 1	184±	6**	189±	**6	$193\pm$	10**	198±	11**	$203\pm$	12**	$207\pm$	12**	
Significant difference ;	*:P≤0.05		★ : P ≤ 0.01				Test of Dunnett	Junnett							

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ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : FEMALE	l j [F344/DuCr j]		ALL ANTMALS				PAGE : 10
Group Name	Administration week 42	ion week 46	50	54	58	62	66
Control	227± 14	231± 15	235 ± 15	239土 16	243土 16	251土 18	254± 19
100 ppm	226± 13	229± 13	. 234土 15	239土 15	244土 16	252土 17	$258\pm$ 18
200 ppm	222± 13	224土 15*	* 228± 15	234± 15	238± 17	244士 18	$248\pm$ 20
400 ppm	212± 12**	211± 14**	** 217± 13**	222 ± 14*	222± 14**	227土 15**	232土 16**
Significant difference ;	* : P . 0.05	** : P ≦ 0.01		Test of Dunnett			

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

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Administration week 74 78 70 74 78 70 74 78 262± 20 266± 21 270± 22 265± 20 266± 21 270± 22 265± 20 269± 21 275± 25 254± 21 265± 21 265± 22 254± 21 265± 21 265± 22 237± 16** 244± 17** 249± 19**	Administration week 70 78 82 86 90 94 170 70 74 7 7 7 8 9 94 170 265± 20 266± 21 275± 25 271± 25 277± 281± 7 275± 277± 281± 7 281± 277± 281± 7 275± 277± 281± 7 281± 277± 281± 7 275± 277± 277± 281± 7 275± 277± <th>ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : FEMALE</th> <th>i[F344/DuCr j]</th> <th>_</th> <th></th> <th>ALL</th> <th>ANIMALS</th> <th>ALL ANIMALS</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th>PAGE : 11</th>	ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : FEMALE	i[F344/DuCr j]	_		ALL	ANIMALS	ALL ANIMALS									PAGE : 11
262± 20 266± 21 270± 22 271± 25 277± 24 281± 27 277± 281± 27 277± 274± 271± 274± 271± 274± 271± 274± 271± 274± 271± 274± 271± 274± 271± 274±	Control $262\pm$ 20 $266\pm$ 21 $270\pm$ $57\pm$ $21\pm$ $21\pm$ $27\pm$	Group Name	Admini 70	stration v			78		82		. 86		06		94		
265± 20 269± 21 275± 25 281± 26 284± 37 291± 47 279± 254± 21 265± 22 269± 22 274± 22 278± 21 273± 237± 16** 244± 17** 249± 19** 250± 27** 251± 16** 254± 16** 246±	265± 20 $269\pm$ 21 $275\pm$ 25 $281\pm$ 26 $284\pm$ 37 $291\pm$ 47 $279\pm$ $269\pm$ $269\pm$ $279\pm$ $269\pm$ $269\pm$ $279\pm$ $279\pm$ $269\pm$ $269\pm$ $279\pm$ $279\pm$ $269\pm$ $269\pm$ $269\pm$ $269\pm$ $269\pm$ $278\pm$ $269\pm$ $269\pm$ $278\pm$ $26\pm$ <td< td=""><td>Control</td><td>$262\pm$</td><td>20</td><td>266±</td><td>21</td><td>270土</td><td>22</td><td>271±</td><td>25</td><td>277±</td><td>24</td><td>281土</td><td>27</td><td>277±</td><td>30</td><td></td></td<>	Control	$262\pm$	20	266±	21	270土	22	271±	25	277±	24	281土	27	277±	30	
254± 21 262± 21 265± 22 269± 22 274± 22 278± 21 273± 237± 16** 244± 17** 249± 19** 250± 27** 251± 16** 254± 16** 246± 246±	200 ppm $254\pm$ 21 $262\pm$ 21 $265\pm$ $269\pm$ 22 $274\pm$ 21 $213\pm$ $213\pm$ $273\pm$ $213\pm$ $216\pm$ $216\pm$ $216\pm$ $216\pm$ $16+*$ $216\pm$ <	100 ppm	265±	20	269 ±	21	275±	25	281±	26	284±	37	$291\pm$	47	279±	27	
237± 16** 244± 17** 249± 19** 250± 27** 251± 16** 254± 16** 246±	400 ppm $237\pm$ 16** $244\pm$ 17** $249\pm$ 19** $250\pm$ 27** $251\pm$ 16** $254\pm$ 16** $246\pm$ 16**400 ppm100 ppm	200 ppm	$254\pm$	21	262±	21	265土	22	269±	22	274土	22	278土	21	273±	22	
	ificant difference : *:P ≤ 0.05 **:P ≤ 0.01 Test of Dunnett	400 ppm	237±	16**	$244\pm$	17**	$249\pm$	19**	$250\pm$	27**	251±	16**	254土	16**	$246\pm$	16**	
	Illcalle all referee , * . r = 0.00 ** . r = 0.01								E								

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PAGE : 12							t t	BAIS4
(SUMMARY)							Test of Dunnett	
CHANGES			34	24	23	19**		
BODY WEIGHT CHANGES ALL ANIMALS		104	284±	288±	280±	249±		
			31	31	23	2]**	01	
	un week	102	283±	283±	281土	$249\pm$	** : P ≦ 0.01	
Ē	Administration week		31	31	29	18**	0. 05	
ij[F344/DuCr]	Admin	98	282±	282±	274土	248±	* : P ≦ 0.05	
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : Al 104 SEX : FEMALE	Group Name		Control	100 ppm	200 ppm	400 ppm	Significant difference ;	(HAN260)

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TABLE E1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : MALE

	Ö	Control		100 ppm	E		200 ppm	UI II		400 ppm	mdd
Ā	Av. FC. 1	No. of	Av. FC.	% of	No. of	Av. FC.	% of	No. of	Av. FC.	% of	No. af
	Ñ	Surviv.		cont.	Surviv.		cont.	Surviv.		cont.	01
	(5)	6		<50>			<50>			<20>	
–	3	50/50	1	66	50/50	14.1 (50)	67	50/50	13.1 (50)	6	50/50
Ē		50/50	16.5 (50)	102	50/50		101	50/50	-	96	50/50
÷.		50/50		101	50/50		98	50/50		06	50/50
;	17.1 (50)	50/50		<u>98</u>	50/50		96	50/50	-	88	50/50
⊣ ÷	L(.3 (50)	50/50		66	50/50	16.7 (50)	67 20	50/50	-	91	50/50
		50/50	10. / (50) 17 9 (E0)	66 00	50/50		86	02/09		16	50/50
- ÷-		50/50	17 D (50)	66 00	30/30 50/50		90 06	50/50 50/50	16.0 (50) 15.0 (50)	26	50/50
(<u></u>	0	50/50	17.1 (50)	26	50/50		06	50/50		6	50/50 50/50
Η		50/50	-	97	50/50		95	50/50		6	50/50
-		50/50	-	96	50/50		97	50/50	_	92	50/50
Ĩ	-	50/50		66	50/50	15.8 (45)	96	50/50	_	92	50/50
ĩ	16.7 (50)	50/50		86	50/50		96	50/50	_	93	50/50
Ĩ		50/50	15.8 (50)	8 6	50/50		94	50/50	_	16	50/50
i		50/50		66	50/50		95	50/50	-	93	50/50
≓;		50/50		101	50/50		96	50/50	15.5 (50)	93	50/50
	16.2 (50)	50/50 50/50		100	50/50		86	50/50	-	94	50/50
		50/50	10.5 (5U) 16 5 (5A)	001	50/50 50/50	16.2 (50)	86	50/50 50/50		93 93	50/50
- ÷-		50/50		<i>ee</i> 02	50/50		90 06	30/30 50/50	15.0 (50)	6 <u>6</u>	50/50 50/50
	17.2 (50)	50/50	17.0 (49)	66	49/50	16. 4 (50)	95 95	50/50		76 76	06/06 50/50
1		50/50		66	49/50		97	50/50		76 63	50/50
Т		50/50		101	49/50		96	50/50	-	94	50/50
-		50/50		66	49/50		98	49/50	-	95	50/50
٦		50/50		101	49/50		96	49/50	-	94	50/50
-	17.3 (50)	50/50		66	49/50		96	49/50	16.0 (50)	92	50/50
-		50/50		100	49/50		66	49/50		95	50/50
-		49/50		66	49/50		96	49/50	_	92	50/50
-		49/50		98	49/50		97	49/50	-	92	50/50
1		49/50		101	49/50		98	49/50	-	95	49/50
1		49/50		100	49/50		66	48/50	-	93	47/50
Ĩ		48/50		66	48/50		86	48/50	<u> </u>	94	45/50
		47/50	17.1 (46)	66	46/50	16.5 (47)	95 2	47/50	с. С.	6 4	45/50
		45/50		2 <u>6</u>	44/50	_	94	46/50	<u> </u>	89	45/50
1		43/50	-	97 2	43/50	-	67	43/50	<u> </u>	95	43/50
i	16.6 (43)	43/50	16.4 (40)	66	40/50	16.9(41)	102	41/50	15.6 (42)	94	42/50
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(BI0040)

BAIS 4

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TABLE E2

and a second

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS : FEMALE

FC. No. of -Ar. FC. % of No. of Ar. FC. % of No. of No No	No. of Surviv.
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	50/50
4 500 501	50/50
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3 $50/50$ 11.1 $50/50$ 11.1 $50/50$ 11.1 $50/50$ 11.1 $50/50$ 11.0 $50/50$ 4 $50/50$ 11.0 $50/50$ 11.0 $50/50$ 11.0 $50/50$ 4 $50/50$ 11.0 $50/50$ 10.0 $50/50$ 10.7 $50/50$ 10.7 $50/50$ 5 $50/50$ 11.0 $50/9$ $50/50$ 10.7 $50/50$ 10.7 $50/50$ 5 $50/50$ 10.8 $50/70$ 10.7 $50/9$ $90/50$ 10.4 $50/50$ 5 $50/50$ 10.7 $50/9$ $90/50$ 10.4 $50/50$ 5 $50/50$ 10.7 $50/9$ $90/50$ 10.4 $50/50$ 5 $50/50$ 10.8 $50/50$ 10.1 $50/50$ 10.1 $50/50$ 5 $50/50$ 10.9 $50/50$ 10.1 $50/50$ 10.2 $50/50$ 5 $50/50$	50/50
4 600 $50/50$ 11.4 500 $50/50$ 11.1 500 $50/50$ 11.0 500 4 500 $50/50$ 11.0 500 96 $50/50$ 10.6 500 4 500 $50/50$ 11.0 500 96 $50/50$ 10.4 500 5 $50/50$ 11.0 500 96 $50/50$ 10.4 500 5 $50/50$ 11.0 500 96 $50/50$ 10.4 500 5 $50/50$ 11.0 500 91 $50/50$ 10.1 500 5 $50/50$ 10.2 500 910 $50/50$ 10.1 $50/50$ 6 500 500 10.0 $50/50$ 10.1 $50/50$ 10.1 $50/50$ 6 500^{50} 10.6 500 97 $50/50$ 10.2 500^{50} 10.2 500^{50}	50/50
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(49) $49/50$ 12.3 500 100 $50/50$ 11.2 483 (49) $49/50$ 12.2 500 104 $50/50$ 11.2 483 (49) $49/50$ 12.2 500 104 $50/50$ 11.7 483 (48) $48/50$ 12.2 500 102 $50/50$ 11.7 483 (48) $48/50$ 12.2 500 100 $50/50$ 11.7 483 (48) $48/50$ 12.2 500 100 $50/50$ 11.7 483 (46) $46/50$ 12.2 500 100 $50/50$ 11.7 483 (45) $48/50$ 11.8 500 99 $50/50$ 11.6 483 (46) $46/50$ 11.8 500 99 $50/50$ 11.2 483 (45) $45/50$ 12.2 477 101 $47/50$ 11.2 477 (44) $44/56$ 12.2 477 <td>48/50</td>	48/50
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3 435 12.5 500 102 $50/50$ 11.7 435 2 438 $48/50$ 12.2 500 100 $50/50$ 11.7 438 1 465 12.2 500 100 $50/50$ 11.6 438 1 465 12.2 507 100 $50/50$ 11.6 438 1 465 12.2 477 101 $47/50$ 12.0 499 $50/50$ 11.2 477 4 455 12.2 477 101 47750 12.4 497 47750 11.4 441 1 443 4750 12.4 497 9750 12.6 442 100 49750 11.6 443 1 4250 12.6 410 96 46750 12.0 441 1 43750 12.4 49750 11.6 <td< td=""><td>48/50</td></td<>	48/50
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4 (4z) 4z/50 13.4 (39) 100 39/50 12.6 (45) 94 45/50 11.9 (41)	44/50
	41/50
(39) 39/50 13.2 (38) 101 38/50 13.0 (43) 99 43/50 11.6 (39)	39/50
13.1(36) 99 $36/50$ $12.4(43)$ 94 $43/50$ $11.6(36)$	36/50
< >:No. of effective animals, ():No. of measured animals Av.FC.: g	

MEAN FOOD CONSUMPTION (FC) AND SURVIVAL

STUDY NO. : 0675 ANIMAL : RAT F344/bucrlcrlj[F344/bucrj] UNIT : g

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TABLE E3

FOOD CONSUMPTION CHANGES : MALE

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SEX : MALE	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-					FAGE :
ameri duo to	Administration week	1 week 2	e	4	5	9	L
Control	14.5± 0.8	16.2± 1.1	16.7± 1.0	17.1± 1.1	17.3± 1.0	16.9± 1.0	17.4土 1.0
100 ppm	14.4士 0.7	16.5土 1.0	16.9士 0.8	16.8土 0.9	17.2± 0.9	16.7± 0.9	17.3土 1.0
200 ррп	14.1± 0.9	16.3± 1.2	16.4土 1.0	16.5± 1.1*	16.7± 0.9**	16.5± 1.0	16.7土 0.9**
400 ppm	13.1± 0.7**	15.5± 1.1**	15.0土_0.8**	15.1± 1.0**	15.7土 0.9**	15.4士 0.9**	16.0土 0.8**
Significant difference ;	*:P≤0.05	** : P ≦ 0.01		Test of Dunnett			

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Group Name	Administration week	1 week					
	8	6	10	11	12	13	14
Control	17.1± 1.0	17.6± 0.9	17.0± 1.0	17.0± 0.9	16.4 ± 1.0	16.7± 0.9	16.2± 0.8
100 ppm	17.0± 1.0	17.1土 0.9*	16.5± 0.9*	16.7土 1.0	16.2土 1.0	16.4土 0.9	15.8土 0.9
200 ppm	16.4± 1.0**	17.0土 1.0**	16.2土 0.9**	16.5± 1.0*	15.8± 0.9**	16.1± 1.0**	15.2士 1.1**
400 ppm	15.9± 0.8**	15.9土 0.8**	15.5土 0.9**	15.6± 0.9**	15.1± 1.0**	15.5± 0.8**	14.8土 0.9**
Significant difference ;	*:P≤0.05	★* : P ≦ 0.01		Test of Dunnett			

Group Name	Administration week	week					
	18	22	26	30	34	38	42
Control	16.4± 1.1	16.6土 1.1	16.2± 0.9	16.5 ± 1.0	16.6± 1.0	17.3士 1.1	17.2土 1.1
nucu 100	16.3± 1.3	16.7± 1.9	16.2± 1.0	16.5± 1.0	16.5± 1.0	16.8± 1.0	17.0± 0.8
200 ppm	15.6土 0.8++	16.0土 1.0*	15.9土 1.0	16.2土 0.9	16.3± 1.0	16.6土 1.1**	16.4士 1.1**
400 ppm	15.3土 1.0**	15.5土 1.1**	15.2± 1.0**	15.4士 1.2**	15.8± 1.0**	15.9± 1.0**	15.9± 1.0**
Significant difference ;	+ : P ≤ 0.05	** : P ≦ 0.01		Test of Dunnett			

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SEX : MALE							PAGE :
Group Name	Administration week. 46	week 50	54	58	62	66	70
Control	16.9± 1.0	17.0± 0.8	17.0± 1.0	17.0± 1.1	17.3± 0.9	17.0± 1.0	17.1± 1.0
100 ppm	16.7土 1.0	17.1± 0.8	16.9土 0.9	17.2± 1.6	17.2± 0.8	17.0土 0.9	17.0± 1.1
200 ppm	16.4± 0.9*	16.4± 0.9**	16.7土 0.9	16.4土 1.0*	16.6± 0.9∗∗	16.8土 1.4	16.5土 0.9*
400 ppm	15.7± 1.0**	15.9± 1.1**	16. 1± 0. 9++	15.9土 1.0**	16.0± 1.2 * *	16.1± 0.9 * *	15.8± 1.1**
Significant difference ;	* : P ≦ 0.05	* * : P ≦ 0.01		Test of Dunnett			

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SEX : MALE							
Group Name	Administration week 74	n week 78	82	86	06	94	86
Control	17.2± 0.8	16.8 ± 1.3	16.6± 1.1	16.9± 1.5	17.3± 1.4	17.0± 2.0	16.2土 1.7
100 ppm	16.9± 0.8	17.0土 0.9	16.6± 1.7	16.8± 1.1	17.1± 1.2	16.7土 1.4	15.7土 1.9
200 ррш	16.6± 1.2*	16.5± 1.0	16.4± 1.0	16.5± 1.0	16.5± 1.9*	15.9士 1.8**	15.7士 2.2
шаа 004	15.8± 1.3**	16.0± 1.4**	15.4土 1.5**	15.9± 1.3*	16.3± 1.7**	15.1土 1.3**	15.4± 1.2
Significant difference :	* N 0.05	* 5 0.01		Test of Numett			

PAGE :						lett	
FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS		16.4土 2.9	E 1.7	16.8土 2.0	15.5士 1.7**	0.01 Test of Dunnett	
	tion week 104	16. 4±	16.5土	16.8±		++ : P ≦ 0.01	
(crlCrlj[F344/buCrj]	Administration week 102	16.6土 3.2	16.4± 2.7	16.9 ± 1.8	15.6土 1.1**	nce ; * : P ≦ 0.05	
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : A1 104 SEX : MALE	Group Name	Control	100 ppm	200 ppm	400 ppm	Significant difference ;	(HANPEN)

TABLE E4

FOOD CONSUMPTION CHANGES : FEMALE

PAGE : 7

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : Al 104 SEX : FEMALE

Group Name

	7	11.3± 1.1	11.1 ± 0.9	11.1± 0.8
	Q	11.7 ± 1.1	11.3土 1.0*	11.6 ± 1.0
	5	11.7± 0.7	11.6 ± 0.8	11.3土 0.7*
	4	11.7± 1.2	 11.2± 0.8*	11.3 ± 0.9
	ŝ	11.4 ± 0.8	 11.2± 0.7	11.3土 0.8
	2	12.1± 1.1	11.8T U.8	12.1± 1.1
Administration week	1 	10.9± 0.6	6.0 ±1.01	10.6土 0.5*

	BAIS 4
Test of Dunnett	
** : P ≦ 0.01	
Significant difference ; * : P \leq 0,05	
Significa	(HAN260)

10.8± 0.8**

10.8± 0.8**

11.0± 0.8**

10.5± 0.7**

10.4± 0.7**

11.8± 1.0

10.0± 0.5**

400 ppm

200 ppm

38

100 ppm

Control

Group Name	Administration week	n week					
	8	6	10	11	12	13	14
Control	11.4± 1.1	11.4± 1.0	11.4± 1.1	11.3± 0.8	11.6± 1.1	, 11.2± 0.9	11.6± 1.3
100 ppm	11.4± 1.1	11.0± 0.8	. 11.0土 0.9	11.1± 0.7	10.8± 0.9**	11.0土 0.6	10.6± 0.8**
200 ppm	11.1± 1.2	10.9土 0.8**	11.2± 1.1	10.7± 0.8**	10.6± 0.9**	10.7土 0.7**	10.5± 0.9**
400 ppm	11.0± 1.0	10.6± 0.8**	10.7土 1.1**	10.5± 0.8**	10.4± 0.8**	10.4士 0.9**	10.1土 1.1**
Significant difference ;	* : P ≤ 0.05	★ : P ≦ 0.01		Test of Dunnett			

Group Name	Administration week	n week					
	18	22	26	30	34	38	42
Control	10.8± 1.2	11.1± 1.2	10.8土 0.7	11.1± 1.1	11.4 ± 1.0	11.9± 1.1	11.6± 1.2
100 ppm	10.8± 0.9	10.9士 1.0	10.9± 1.0	11.0土 0.9	11.5士 0.9	11.5± 1.1	11.8± 1.0
200 ррш	10.5± 0.9	10.6土 0.9	10.5土 0.9	10.8± 0.8	11.1± 0.9	11.0土 0.8**	11.3± .1.0
400 ppm	10.3 ± 1.0	10.5士 1.0*	10.2土 0.7**	10.8± 1.1	,10.8土 0.9##	11.2士 1.0**	11.0土 1.0*
Significant difference ;	* : P ≤ 0.05	★ : P ≤ 0.01		Test of Dunnett			

	week
0675 RAT F344/DuCrlCrlj[F344/DuCrj] g : Al 104 3	Administration week
STUDY NO. : 0675 ANTMAL : RAT F344. UNIT : g REPORT TYPE : A1 104 SEX : FEMALE	Group Name

FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS

46 50 54 58 62 66 ntrol 11.7± 0.9 11.9± 1.1 11.4± 1.0 11.7± 1.0 11.7± 1.2 1.1	Group Name	Administration week	n week					
$11.7\pm$ 0.9 $11.9\pm$ 1.1 $11.4\pm$ 1.0 $11.7\pm$ 1.1 $11.7\pm$ 1.1 $11.7\pm$ $1.7\pm$ 1.1 $11.7\pm$ $1.7\pm$ 1.2 1.1 $1.7\pm$ 1.2 1.0 $1.2.2\pm$ 1.0 $1.2.2$ 1.0 $1.2.2$		46		54	58	62	66	70
11.7± 0.9 11.9± 1.1 11.4± 1.0 11.7± 1.1 11.7± 1.2 11.5± 1.0 11.7± 0.7 11.3± 1.1 12.0± 0.9 12.3± 1.0 12.2± 1.0 11.3± 1.1 11.4± 0.7* 11.3± 0.8 11.5± 0.8 11.7± 0.8** 11.8± 1.2 11.3± 1.1 11.3± 0.8 11.5± 0.8 11.7± 0.8** 11.8± 1.2 10.8± 0.7** 11.3± 1.0** 11.6± 1.5 10.8± 0.8** 11.7± 0.8** 11.7± 1.2 *: P ≤ 0.05 **: P ≤ 0.01 15.5± 0.8** 11.2± 0.9** 11.7± 1.2								
11.5± 1.0 11.7± 0.7 11.3± 1.1 12.0± 0.9 12.3± 1.0 12.2± 1.0 11.3± 1.1 11.4± 0.7* 11.3± 0.8 11.5± 0.8** 11.8± 1.2 10.8± 0.7** 11.3± 10.8± 0.8** 11.2± 0.9** 11.7± 1.2± 1.2 *: P ≤ 0.05 *: P ≤ 0.01 Test of Durnett Test of Durnett Test of Durnett Test of Durnett	Control	11.7± 0.9	11.9± 1.1	11.4± 1.0	11.7± 1.0	12.3± 1.1		12.3± 1.1
11.3 ± 1.1 $11.4\pm 0.7*$ 11.3 ± 0.8 11.5 ± 0.8 $11.7\pm 0.8**$ 11.8 ± 1.2 $10.8\pm 0.7**$ $11.3\pm 1.0**$ 11.6 ± 1.5 $10.8\pm 0.8**$ $11.2\pm 0.9**$ 11.7 ± 1.2 $*: P \le 0.05$ $*: P \le 0.01$ Test of Durnett	100 ppm	11.5± 1.0	11.7± 0.7	11.3± 1.1		12.3± 1.0		12.5± 1.1
$10.8\pm 0.7^{**} 11.3\pm 1.0^{**} 11.6\pm 1.5 10.8\pm 0.8^{**} 11.2\pm 0.9^{**} 11.7\pm 1.2$ $*: P \leq 0.05 **: P \leq 0.01$	200 mqq	11.3± 1.1				11.7± 0.8**		11.8± 0.9*
*:P≦0.05 **:P≦0.01 Test of Dunnett	400 pm	10.8± 0.7**	11.3± 1.0**			11.2± 0.9**		11.7± 0.8**
*:P≦0.05 **:P≦0.01 Test of Dunnett								
	Significant difference ;		** : P ≦ 0.01		Test of Dunnett		And the second se	

	Administration wook	hoor					
	54 54	78	82	86	96	94	86
Control	12.2± 1.2	12.1± 1.0	12.1± 1.1	12.4± 1.2	13.1± 1.7	12.1± 1.6	13.4土 1.4
100 ppm	12.2± 0.8	12.3± 1.8	12.2± 1.3	12.5± 2.2	13.1± 1.0	12.0± 1.1	13.4± 1.4
200 ppm	12.1± 0.9	11.8± 1.0	12.0± 1.0	12.4± 1.1	12.7± 1.2	11.6土 1.2	12.6± 2.2
400 ppm	11.6± 0.9**	11.6± 1.2*	11.2± 0.9**	11.4± 0.8**	12.0土 1.0**	10.6土 1.0**	11.9 ± 1.6 **
Significant difference; *	* : P ≦ 0.05	* : P ≤ 0.01		Test of Dunnett			

STUDY NO. : 0675 ANTMAL : RAT F344/DuCrlCrlj[F344/DuCrj] UNIT : g REPORT TYPE : Al 104	j[F344/DuCr.j]	1	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS
SEA · FEMALE Group Name	Administration week 102	on week104	PAGE : 12
Control	13.1± 1.7	13.2± 1.1	
100 ррш	13.2 ± 1.5	13.1± 1.3	
200 ppm	13.0± 1.3	12.4± 1.2*	
. 400 ppm	11.6± 1.2**	11.6土 1.2**	
Significant difference;	*:P≤ 0.05	₩ : P ≦ 0.01	Test of Dunnett
(HAN260)			BAIS 4

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TABLE F1

HEMATOLOGY : MALE

ANLMAL : KAI F344/DuCrJJ[F344/DuCrJ] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	r344/DUULIULI 1 REPORT	NUCLUELJ LE344/ DUCEJ) REPORT TYPE : Al											PAGE :
Group Name	NO. of Animals	RED BLOOD CELL 1 Ο ⁵ /μℓ	BMOGLOBIN g ∕dℓ	HEM %	HEMATOCRIT %	MCV f <i>Q</i>		MCH P g		MCHC g / dl		PLATELET 1 0 ³ / µl	LL LL
Control	40	7.59± 1.26	12.7± 2.5	5 36.2±	+ 6.1	47.7土	3.1	16.7±	1.6	34.9土	1.7	1170±	413
100 ppm	39	7.78± 1.43	13.0土 2.6	6 37.0±	÷.0	4 8. 3±	6.3	$16.8\pm$	2.3	34.8±	2.0	$1101\pm$	421
200 ppm	39	7.99±_0.99	13.6土 1.9	9 37.9∓	4.5	47.5土	2.0	17.0±	1.1	35.7±	1.2*	$1048\pm$	288
400 ppm	42	8. 05± 1. 26	13.6土 2.6	6 38.2±	i± 6.0	$47.5\pm$	2.8	16.9±	1.5	35.4土	1.8*	1078±	319
Significant c	Significant difference ;	* : P ≤ 0.05	** : P ≦ 0.01			Test of Dunnett	hett						

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1	344/DuCr1Cr1j	[F344/DuCr j]	HEMATOLOGY (SUMMARY) ALL ANIMALS (1059)	
SEX : MALE	REPORT TYPE : A1	rpe : A1		PAGE : 2
Group Name	NO. of Animals	RETICULOCYTE %		
Control	40	5.0+ 2.7		
100 ppm	39	5.5± 5.6		
200 ppm	39	3.9± 1.7		
400 ppm	42	4.7土 2.6		
Significant difference ; *: $P \leq 0.05$	ifference;	*:P≤0.05	++ : P ≦ 0.01	Test of Dunnett
(HCL070)				BAIS 4

Group Name N0. of Animals WBC I $0^{2}/\mu\ell$ Differential NUMD WBC LVMPHO Differential LVMPHO WBC MONO Differential EOSINO MSO Differential EOSINO Differential EOSI	SIUNT NO. : 0675 ANTMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	344/DuCr1Cr1 REPORT	uCrlCrlj[F344/buCrj] REPORT TYPE : Al		ALL ANIMALS (1054)	5W)								PAGE :
40 $6.57\pm$ 2.28 $50\pm$ 9 $41\pm$ 8 $6\pm$ 2 1± 1 $0\pm$ $0\pm$ $0\pm$ $2\pm$ 39 $6.83\pm$ 1.88 $48\pm$ 7 $43\pm$ 6 $6\pm$ 1 $1\pm$ 1 $0\pm$ 0 $1\pm$ 39 $11.45\pm$ 20.74 $50\pm$ 11 $39\pm$ 12 $6\pm$ $1\pm$ $1\pm$ $1\pm$ $0\pm$ $0\pm$ $4\pm$ 42 $10.34\pm$ 20.57 $50\pm$ 11 $40\pm$ 10 $5\pm$ 2 $1\pm$ $0*$ $0\pm$ 1 $4\pm$		NO. of Animals	₩BC 1 0 ³ ∕ μℓ	Differentia. NEUTRO	MPF	ONOW	Η	GOSINO		BASO		OTHER		
39 6.83± 1.88 48± 7 43± 6 6± 1 1± 1 0± 0 1± 39 11.45± 20.74 50± 11 39± 12 6± 1 1± 1 0± 0 4± 42 10.34± 20.57 50± 11 40± 10 5± 2 1± 0* 0± 1 4±	Control	40				6 ±	62	+ -	1	+1	0	5+	1	
39 11.45± 20.74 50± 11 39± 12 6± 1 1± 1 0± 0 4± 42 10.34± 20.57 50± 11 40± 10 5± 2 1± 0* 0± 1 4±	100 ppm	39				1 9	1	+	1	+1 0	0	1+	I	
42 10.34 \pm 20.57 50 \pm 11 40 \pm 10 5 \pm 2 1 \pm 0* 0 \pm 1 4 \pm	200 ppm	39	11. 45± 20. 74			9	1	1+ 1+	1	+0	0	4 +	14	
	400 ррт	42	10.34± 20.57			5±	5	1+ 1+	*0	+1	1	4+	14	
Significant difference ; *:P ≤ 0.05 +*:P ≤ 0.01 Test of Dunnett	Significant di	fference ;	* : P ≤ 0.05	** : P ≦ 0.01		Test	of Dunnett							

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TABLE F2

HEMATOLOGY : FEMALE

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NEASURE TIME : 1 NEASURE TIME : 1 SEX : FEMALE REPORT TYPE : A1	REPORT	REPORT TYPE : A1												PAGE :
Group Name	NO. of Animals	RED BLOOD CELL 1 O ⁵ /µl	hemoglobin g ⁄ðl	IJ	HEMATOCRIT %	LIS	MCV f <i>R</i>		MCH p g		MCHC g ⁄ dℓ		PLATELET 1 0 ³ / µl	ST Le
Control	37	7.80土 1.28	14.5±	2.0	39.1±	4.7	50.9土	5. 6	18.8土	1.6	37.0±	1.5	728±	168
100 ppm	36	8.04士 0.66	14.9±	1.2	39.9 ⊥	2.9	49.7±	2.0	18.6±	0. 7	37.4±	0.7	688土	108
200 ppm	42	8.13土 0.56	15.0土	1.0	$40.0\pm$	2.6	4 9. 2±	1.4	18.5±	0. 7	37.5±	0.8	725土	137
400 ppm	36	8.09土 0.75	$15.2\pm$	1.1	40.6土	2.4	50.5±	3.8	18.8±	1.0	37.3±	0.8	765土	169
Significant difference ;	ifference ;	* : P ≤ 0.05	★ : P ≤ 0.01				Test of Dunnett	lett						

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SIUNT NU. : U6/5 ANTMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE, TIME : 1	F344/DuCr1Cr1 1	j[F344/DuCrj]	ALL	ALL ANTMALS (105#)	
FEMALE	REPORT	TYPE : Al			PAGE : 5
Group Name	NO. of Animals	RETICULOCYTE %			
Control	37	4. 0± 5. 6			
ndd 100	36	2.6士 1.4			
200 ppm	42	2.6士 1.6			
400 ppm	36	3.3± 3.9			
gnificant (Significant difference ;	*:P≦0.05	★★ : P ≦ 0.01	Test of Dunnett	
(HCL070)					BAIS 4

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Group Name NO. of WBC Animals 10 ³ /ub	MEASURE: TIME : 1 SEX : FEMALE REPORT TYPE : A1		ALL ANIMAI	ALL ANIMALS (105W)									PAGE :
		Differential WBC NEUTRO LY	WBC (%) LYMPHO		ONOW		EOSINO		BASO		OTHER		
Control 37 4.49± 5.	5.41	38± 11	53±	12	5 1+	5	2±	1	+0	0	+ -	1	
100 ppm 36 4.01± 2.	2. 88	38±	52±	10	5	5	2+	1	+0	1	5+	വ	
200 ppm 42 3.88± 1.	1.75	39± 7	52±	2	ا+ ئ	5	$^{2+}$	1	+1	0	1+ 1+	1	
400 ppm 36 3.24± 0.	0.98	42± 7	51+	7	5 +	1	5 1+	1	+1 0	0	+	0	·
Significant difference ; *: P ≤ 0.05	0. 05	** : P ≦ 0.01			Test o	Test of Dunnett							

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TABLE G1

BIOCHEMISTRY : MALE

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MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	REPORT	REPORT TYPE : A1													PAGE :
Group Name	NO. of Animals	TOTAL PROTEIN g∕dℓ	ROTEIN	albumin g ⁄dl		A/G RATIO	IO	T-BILIRUBIN ng∕dℓ	RUBIN	GLUCOSE mg/dl		T-CHOLESTEROL mg∕dℓ	STEROL	TRIGLYCERIDE mg/dl	CERIDE
Control	40	6.8±	0.4	2.8±	0.3	0.7±	0. 1	0.14±	0. 03	147土	30	192±	52	131土	88
100 ppm	39	6.8±	0.4	2.9±	0.2	0.7±	0.1	0.48±	2. 06	160土	19	186±	66	$140\pm$	66
200 ppm	40	6.8±	0.3	2.8±	0.3	0.7±	0.1	0.14±	0. 03	152±	25	194±	76	139±	94
400 ppm	42	6.8+	0.3	2.8±	0.2	0.7±	0. 1	0.16±	0.04	155±	15	193±	64	135±	92
Significant difference ;	ifference ;	*:P≤0.05		★ : P ≦ 0.01				Test of Dunnett	nnett						

ANLMAL : KAT F344/DuCr1J1F344/DuCr1J MEASURE. TIME : 1 SEX : MALE REPORT TYPE : AI	REPORT	REPORT TYPE : A1			1										PAGE : 2
Group Name	NO. of Animals	alallohqsohq digilohqsohq	IPID	AST IU⁄£	E	ALT I U / L		LDH IU⁄£	e	ALP I U / L	ę	6-GTP I U∕ℓ		cK IU∕ℓ	
Control	40	279±	69	91±	88	37±	19	140±	44	335±	131	8 +	10	111±	45
100 ppm	39	$272\pm$	86	$116\pm$	251	40±	42	148±	06	351±	175	8	വ	$108\pm$	31
200 ppm	40	275±	96	78±	26	35土	12	155±	149	321±	81	11	4	$113\pm$	52
400 ppm	42	274土	84	73±	27	34土	6	157±	150	$332\pm$	58	+ 6	<u>4</u> **	108土	40
Significant difference ; *: P ≦ 0.05	ifference ;	* : P ≤ 0.		★ : P ≦ 0.01	I.			Test of Dunnett	nett						

ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1 SEV : MATE	/DuCrlCrlj	ilF344/DuCrj.	_		ALL	ALL ANIMALS (105W)	5W)								
DEA • MALE	KEPUKI	KEPUKI IYPE : AI													PAGE : 3
Group Name NC	NO. of Animals	UREA NITROGEN mg/dℓ	rrogen	CREATININE ™g∕dℓ	INE	SODIUM mEq∕£		POTASSIUM mEq∕£	r Lum	CHLORIDE m Eq ∕ 2	(7)	CALCIUM mg/dl		INORGAN mg⁄dℓ	INORGANIC PHOSPHORUS
						-									
Control	40	21.1±	7.3	0.6±	0.1	$142\pm$	1	3.8±	0.4	$106\pm$	2	10.5土	0.6	4. 3±	1.0
100 ppm	36	20.6土	5.8	0.6±	0.2	143土	2	3.8±	0.3	106±	2	10.4±	0.5	4.4士	0.9
200 ppm	40	20.6±	6.0	0.6±	0.1	142±	1	3.7±	0.5	$106\pm$	2	$10.5\pm$	0.4	4.3+	0.8
400 ppm	42	20.1±	3.9	0.6±	0.1	142±	1	3.9±	0.3	106土	2	10.4±	0.4	4.5±	0.6
Significant difference ; * : P ≤ 0.05	srence ;	* : P ≤ 0.		* : P ≦ 0.01	1			Test of Dunnett	unett						

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TABLE G2

BIOCHEMISTRY : FEMALE

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MEASURE. TIME : 1 SEX : FEMALE REPORT TYPE : AI	1 REPORT	REPORT TYPE : A1	L.												PAGE :
Group Name	NO. of Animals	TOTAL PROTEIN g ∕dℓ	ROTEIN	ALBUMIN g ⁄dl		A/G RATIO	10	T-BILIR mg/dl	T-BILIRUBIN mg∕dℓ	GLUCOSE mg/dl		T-CHOLESTEROL mg/df	STEROL	TRIGLYCERIDE mg/dl	ERIDE
Control	38	7.2土	0.5	3.6±	0.3	1.0±	0.1	0.15±	0.20	142±	21	156±	41	123±	101
100 ppm	36	7.3±	0.4	3.5±	0.3	1. 0 <i>±</i>	0.1	0.15±	0. 08	$140 \pm$	15	$165\pm$	49	142±	115
200 ppm	42	7.2±	0.4	$3.5\pm$	0.3	$0.9\pm$	0.1	0.13±	0. 02	142±	14	$161\pm$	49	$107\pm$	88
400 ppm	36	7.2±	0.4	, 3.6±	0.3	1.0±	0.1	0. 13⊥	0.01	144±	15	155±	39	63±	58**
Significant difference ;	lifference ;	* : P ≦ 0.05		** : P ≦ 0.01				Test of Dunnett	unett	1.11.11.11.11.11.11.11.11.11.11.11.11.1					

ANIMAL : RAT F344/DuCrICr1j[F344/DuCrj] MEASURE, TIME : 1 SEX : FEMALE REPORT TYPE : A1	344/ DUUTIUTI	REPORT TYPE : AI	7		4										PAGE :
Group Name	NO. of Animals	JP∕3W GIAITOHASOHA	LIPID	AST I U / <i>e</i>		ALT I U / 2		LDH LU/2	2	ALP I U / L	5	G-61P 1 U ∕ £		cK IU∕£	2
Control	38	290±	74	118±	59	51±	35	155±	11	189土	65	3 + 2	1	7 96	22
100 ppm	36	299±	87	192土	256	64土	45	167±	119	238±	169	3±	ę	$102\pm$	68
200 ppm	42	286±	83	134±	06	59±	28	147±	49	221±	84	3+	53	$91\pm$	21
400 ppm	36	275土	68	108土	42	52±	23	138±	50	185±	55	3±	ц	± 16	25
Significant difference ; *: P ≦ 0.05	ifference ;	* : P 10.	05	* : P ≦ 0.01				Test of Dunnett	nett	- - 					and many the first of the second

ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] MEASURE. TIME : 1 SEX : FEMALE REPORT TYPE : A1	844/DuCr1Cr1. REPORT 1	uCrlCrlj[F344/DuCrj] REPORT TYPE : Al			mu	(HUUT) CUMBINI UNI									PAGE : 6
Group Name	NO. of Animals	UREA NITROGEN ™g∕dℓ	ĒN	CREATININE mg∕d£	INE	SODIUM mEq∕ 2		POTASSIUM mEq∕£	e B	CHLORIDE m Eq∕ ℓ		CALCIUM mg/dl		INORGAN mg⁄d£	INORGANIC PHOSPHORUS mg/dl
Control	38	17.3± 2.4	4 4	0.6±	0.1	141±	8	3. 3±	0.3	` 103±	ņ	10.6±	0.5	4 . 0±	0.8
100 ppm	36	17.4士 1.8	œ	0.6±	0.1	141±	1	3.4±	0.4	$104\pm$	3	10.7±	0.4	4 . 0±	0.7
200 ppm	42	17.4± 1.9	6	0.6±	0.1	$140\pm$	1	3.4±	0. 4	104土	7	10.6±	0.4	3.9±	0.7
400 ppm	36	19.2± 1.4	1. 8**	0. 6±	0.1	$140\pm$	1	3.5±	0.4	104±	2	10.5±	0.4	4 . 1±	0.7
Significant difference ;	fference ;	* : P ≦ 0.05	 ‡	≭ : P ≦ 0.01				Test of Dunnett	nett		41997				

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TABLE H1

URINALYSIS : MALE

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AGE : 1

Group Name	NO. of Animals	рН 5.0	of pH control of 8.0 8. 10 1.5 8.0 8. 10 1.5 1.0 1.5 1.0 1.5 1.0 1.5 1.0 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5	6.5	7.0	7.5	8.0	8.5 CHI	Protein - ± + 2+ 3+ 4+ C	$\begin{array}{ccc} \text{Glucose} \\ \text{GHI} & -\pm + 2 + 3 + \frac{4}{4} \\ \text{CHI} \end{array}$	Ketone body - 土 + 2+ 3+ 4+ CHI	Bilirubin - + 2+ 3+	PAGE
Control	43	0	1	ŝ	ę	15	21	0	0 0 0 3 24 16	43 0 0 0 0 0	42 1 0 0 0 0	42 1 0 0	
100 ррш	43	0	1	4	2	17	14	0	0 0 0 1 27 15	43 0 0 0 0 0	41 2 0 0 0 0	40 2 0 1	
200 ppm	42	0	0	1	2	22	12	0	0 0 1 3 25 13	42 0 0 0 0 0	40 2 0 0 0 0	42 0 0 0	
400 ppm	42	0	0	, 1	5	14	22	0	0 0 0 4 20 18	42 0 0 0 0 0	33 3 0 0 0 0	42 0 0 0	

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Test of CHI SQUARE

****** : P ≦ 0.01

*:P ≦ 0.05

Significant difference ;

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. 3274						Test of CHI SOUARE
URINALYSIS	Urobilinogen ± + 2+ 3+ 4+ CHI	43 0 0 0 0	43 0 0 0 0	42 0 0 0 0	42 0 0 0 0	** : P ≦ 0.01
buCrlCrlj[F344/DuCrj] REPORT TYPE : Al	0ccult blood - ± + 2+ 3+ CHI	43 0 0 0 0	39 1 0 3 0	42 0 0 0 0	38 1 1 1 1	* : P ≦ 0.05
344/DuCrlCrlj . REPORT 1	NO. of Animals	43	43	42	42	ifference ;
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	Group Name	Control	100 ppm	200 ppm	400 ppm	Significant difference ;

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TABLE H2

URINALYSIS : FEMALE

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SEX : FEMALE			7												PAGE :
Group Name	NO. of Animals	рН 5.0	6.0	6.5	2.0	7.5 8	pH 5.0 6.0 6.5 7.0 7.5 8.0 8.5	5 CHI	Protein - ± + 2+ 3+ 4+ CHI		Glucose Glucose CHI	Ketone body - ± + 2+ 3+ 4+	CHI	Bilirubin - + 2+ 3+	CHI
Control	41	0	ო	5	4]	11	13 8	æ	0 1 6 11 20 3	41 0 0	0 0 0	36 5 0 0 0 0		41 0 0 0	
100 ppm	39	0	0	23	6 1	17	8	ç	0 0 1 9 26 3	39 0	0 0 0 0	32 7 0 0 0 0		39 0 0 0	
200 ppm	44	0	0	1	12 1	14	8	•	0 1 4 12 21 6	44 0 0	0 0 0 0	42 1 1 0 0 0		44 0 0 0	
400 ррп	41	0	0	ŝ	1	11 1	11 9	¢	0 1 6 11 17 6	41 0	0 0 0 0 0	32 6 3 0 0 0		41 0 0 0	
Significant o	Significant difference ;	*	* : P ≦ 0.05	0.05	-	ч Ч Т	* : P ≤ 0.01	01	Tec	Test of CHI SQUARE	JUARE				

	. PAGE : 4						•	BAIS 4
·							Test of CHI SQUARE	
URINALYSIS		Urobilinogen ± + 2+ 3+ 4+ CHI	41 0 0 0 0	39 0 0 0 0	44 0 0 0 0	41 0 0 0 0	** : P ≤ 0.01	
l j [F344/DuCr j]	REPORT TYPE : AI	Occult blood - ± + 2+ 3+ CHI	41 0 0 0 0	36 0 0 1 2	42 0 0 0 2	39 0 1 1 0	* : P ≦ 0.05	
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] MFASTIRF TIME : 1	4	NO. of Animals	rol 41	39 39	19m 44	opm 41	Significant difference ;	
STUDY NO. : 0675 ANIMAL : RAT F MFASTIRE TIME : 1	SEX : FEMALE	Group Name	Control	100 ppm	200 ppm	400 ppm	Sígnifica	(HCL101)

TABLE J1

ORGAN WEIGHT, ABSOLUTE : MALE

REPORT TYPE : A1 SEX : MALE UNIT: g									. DACE .
Group Name NO. of Animals	Body Weight		ADRENALS	TESTES	HEART	ζT	TUNGS	KIDNEXS	
Control 41	391± 52	0.115±	0. 243	3.608± 1.279	279 1.228±	0.116	I. 378± 0.	0.120 2.765 ±	0. 348
100 ppm 39	390 ± 54	0.091±	0.115	3. 517± 1. 402	102 1.245土	0.112	1.416土 0.	0.244 2.860±	0.401
200 ppm 40	381± 51	0. 073±	0.014	3. 101± 1. 306	306 1. 209土	0.104	1. 363± 0.	0.115 2.799±	0. 350
400 ppm 42	352± 19++	0. 079 ±	0.059*	3.673± 1.362	362 1.184土	0.080	1. 339 ± 0.	0.179 * * 2.730±	0. 243
Significant difference ;	: *:P≦0.05	** : P ≦ 0.01			Test of Dunnett				

SPLEEN LIVER BRAIN 1. 052± 0. 463 11. 071± 2. 073 2. 093± 0. 060 1. 328± 1. 926 11. 407± 1. 609 2. 108± 0. 063 1. 328± 0. 371 11. 114± 1. 844 2. 091± 0. 046 1. 138± 0. 843 10. 576± 1. 088 2. 061± 0. 045*	LE TATA AND A TATA AND AND A TATA AND A TATA AND AND AND AND AND AND AND AND AND AN				PAGE
1.052± 0.463 11.071± 2.073 2.093± 0.060 1.328± 1.926 11.407± 1.609 2.108± 0.063 1.328± 0.371 11.114± 1.844 2.091± 0.046 1.028± 0.371 11.114± 1.844 2.091± 0.046 1.138± 0.843 10.576± 1.088 2.061± 0.045*	Group Name	NO. of Animals	SPLEEN	LIVER	
$1.328 \pm$ 1.926 $11.407 \pm$ 1.609 $2.108 \pm$ 0.063 $1.028 \pm$ 0.371 $11.114 \pm$ 1.844 $2.091 \pm$ 0.046 $1.138 \pm$ 0.843 $10.576 \pm$ 1.088 $2.061 \pm$ $0.045*$	Control	41		11. 071± 2. 073	
1.028± 0.371 11.114± 1.844 2.091± 0.046 1.138± 0.843 10.576± 1.088 2.061± 0.045*	100 ppm	39			
1.138±0.843 10.576± 1.088 2.061± 0.045*	200 ppm	40			
	400 ppm	42			
tt : F ≥ 0.01	Significant d	ifference ;	* : P ≤ 0.05 #	# : P ≦ 0.01	Test of Dunnett

TABLE J2

ORGAN WEIGHT, ABSOLUTE : FEMALE

PAGE : 3

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Ϋ́Α						
	SXS	0. 165	0.169	0. 196	0.132*	
	KIDNEYS	1.875±	1.876±	1.851±	1.773土	
	6	0. 131	0. 111	0. 057	0. 060	
	LUNGS	0.970±	0.965±	0. 939土	0.926±	
		0.077	0. 074	0.052	0.066*	
RY)	HEART	0. 889±	0.894±	0.869±	0.843±	Test of Dunnett
TE (SUMMAI 05W)	IES	0. 141	0. 032	0. 443	0. 151	Ţġ
orcan Weicht: Absolute (Summary) Survival Antmals (1059)	OVARIES	0.142±	0. 123±	0.178±	0. 136±	
ORGAN Y SURVIVA	NALS	0. 076	0.009	0.010**	0.017**	
	ADRENALS	0. 089 ±	0. 072±	0. 071±	0. 073±	★★ : P ≦ 0.01
	Body Weight	33	23	21	18**	. 05
lj[F344/DuCrj]	Body	263±	269±	262±	234土	* : P ≤ 0.05
344/DuCr1Cr	NO. of Animals	38	36	42	36	lifference ;
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : A1 SEX : FEMALE UNIT: g	Group Name	Control	100 ррм	200 ppm	400 ppm	Significant difference ; (HCL040)

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STUDY NO. : 0675 ORGAN WEIGHT:ABSOLUTE (SUMMARY) ANTMAL : RAT F344/DuCrICrIj[F344/DuCrj] SURVIVAL ANTMALS (105W) SEX : FEMALE UNTT g PAGE : 4	N0. of SPLEEN LIVER BRAIN Animals	38 0.771土 1.049 6.844土 1.014 1.908土 0.037	36 0.749 \pm 0.673 7.089 \pm 1.214 1.889 \pm 0.048	42 0.567 \pm 0.153 6.896 \pm 0.911 1.889 \pm 0.041	36 0.523土 0.089 6.162土 0.545+* 1.863土 0.037++	difference : $*: P \leq 0.05$ **: $P \leq 0.01$ Test of Dunnett .
344/DuCr1Cr1j	NO. of Animals	38	36	42	36	fference ;
STUDY NO. : 0675 ANTMAL : RAT F3 REPORT TYPE : A1 SEX : FEMALE UNIT: g	Group Name	Control	100 ppm	200 ppm	400 ppm	Significant difference ;

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TABLE K1

ORGAN WEIGHT, RELATIVE : MALE

- - -	1 . GVA					BAIS 4
	KIDNEYS	· 0.723± 0.166	0.748土 0.157	0.745土 0.119	0.778土 0.073**	
·	FUNCS	0. 358± 0. 053	0.372± 0.099	0.364± 0.060	0. 383± 0. 065*	
RY)	HEART	0.319土 0.046	0.325± 0.050	0.321 ± 0.039	0.338± 0.026**	Test of Dunnett
ORGAN WEIGHT:RELATIVE (SUMMARY) SURVIVAL ANIMALS (105W)	TESTES	0.917± 0.304	0.907± 0.351	0.819± 0.341	1.043± 0.382	Tec
SURVI	ADRENALS	0. 030± 0. 064	0.024± 0.032	0.019± 0.004	0.023± 0.017	** : P ≦ 0.01
j[F344/DuCrj]	Body Weight (g)	391± 52	390十 54	381± 51	352± 19++	* : P IA * : • *
F344/DuCr1Cr1	NO. of Animals	41	39	40	42	difference;
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : Al SEX : MALE UNT: %	Group Name	Control	100 ppm	200 ppm	400 ppm	Significant difference ; (HCL042)

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PAGE : 2						BAIS 4
ORGAN WEJGHT: RELATIVE (SUMMARY) SURVIVAL ANIMALS (1054)	BRAIN	0.545± 0.080	0.549 ± 0.063	0.558± 0.072	0.588± 0.033**	Test of Dunnett
ORGAN	LIVER	2.856土 0.548	2.966土 0.555	2.929± 0.404	3.014± 0.323*	# : P ≦ 0.01
i[F344/buCr.j]	SPLEEN	0.272± 0.126	0.362土 0.603	0.274土 0.104	0.331 ± 0.290	* : P ≦ 0.05 #
STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : AI SEX : MALE UNTT: %	Group Name NO. of Animals	Control 41	100 ppm 39	200 ppm 40	400 ppm 42	Significant difference ; .042)
STUD ANIM REPO SEX UNIT	Grou					Sign (HCL042)

TABLE K2

ORGAN WEIGHT, RELATIVE : FEMALE

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NEPORT TITE - AL SEX : FEMALE UNIT: %								PAGE :
Group Name N	NO. of Animals	Body Weight (g)	ADRENALS	OVARIES	HEART	Sound	KIDNEYS	
Control	38	263± 33	0.035± 0.032	0. 055± 0.058	0.343 ± 0.053	0. 377 ± 0. 083	0.726± 0.118	
ndd 100	36	269± 23	0.027± 0.003	0.046± 0.012	0.333± 0.027	0.360 ± 0.047	0.700± 0.070	
200 ppm	42	262土 21	0.027± 0.004	0.068± 0.167	0.333± 0.025	0.360 ± 0.035	0. 709± 0. 088	
400 ppm	36	234± 18**	0.031 ± 0.008	0.058土 0.063**	0.362土 0.029**	0.398± 0.035 * *	0.762二 0.066**	
Significant difference ;	ference ;	* : P ≦ 0.05	₩ : P ≦ 0.01	Test	Test of Dunnett			

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						Test of Dunnett
SURVIVAL ANIMALS (105W)	BRAIN	0.739± 0.104	0.706± 0.058	0.725± 0.060	0.803± 0.067**	Te
TANG STATES	LIVER	2.628± 0.414	2.639土 0.431	2.633 ± 0.314	2.645土 0.215	** : P ≤ 0.01
	SPLEEN	0.311± 0.479	0.280± 0.256	0.217 ± 0.061	0.225 ± 0.038	* : P ≤ 0.05
	NO. of Animals	38	36	42	36	ifference;
REPORT TYPE : A1 SEX : FEMALE UNIT: %	Group Name	Control	100 nad	200 ppm	400 ppm	Significant difference ; (HCL042)

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TABLE L1

HISTOPATHOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : MALE ALL ANIMALS

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STUDY NO. ANIMAL REPORT TYPE SEX	: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : Al : MALE	HISTOPATHOLOGICAL FINDINGS : ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		PAGE : 1
Organ	. Group Name No. of Animals on Study Grade . (9	Control 1 Study 50 (%) (%) (%) (%)	$\begin{array}{ccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$	200 ppm 50 (%) (%) (%) (%)	$\begin{array}{cccc} 400 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$
(Integumenta skin/app	[Integumentary system/appandage] skin/app epidermal cyst			<50>	<pre>< 50></pre>
(Respiratory system)	Y system)			(0) (2) () (0) (0)
nasal cavit	thrombus	<pre> <50> 2 0 0 0 (4) (0) (0) (0)</pre>	<pre> <50> <50> (50) (50) (50) (50) (50) (50) (50) (50)</pre>	$\begin{array}{cccc} <50 \\ 1 & 0 & 0 \\ (2) & (0) & (0) \\ \end{array} \right)$	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>
	mineralization	38 0 0 0 0 (0) (10) (10) (10) (10) (10) (1	43 0 0 0 (86) (0) (0) (0)	41 0 0 0 (82) (0) (0) (0)	39 1 0 0 (78) (2) (0) (0)
	eosinophilic change:olfactory epithelium	36 11 0 0 (72)(22)(0)(0)	44 3 0 0 (88) (6) (0) (0)	41 2 0 0 * (82) (4) (0) (0)	41 1 0 0 ** (82) (2) (0) (0)
	eosinophilic change:respiratory epithelium	12 0 0 0 (24)(0)(0)(0)	16 0 0 0 (32)(0)(0)(0)	11 0 0 0 (22)(0)(0)(0)	10 0 0 0 (20) (0) (0) (0)
	inflammation:foreign body	10 0 0 0 0 (20) (20) (0) (0)	18 2 0 0 (36)(4)(0)(0)	14. 1 0 0 (28) (2) (0) (0)	10 2 0 0 (20)(4)(0)(0)
	inflammation:respiratory epithelium	3 1 0 0 (6)(2)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	14 2 0 0 ** (28) (4) (0) (0)	22 2 0 0 ** (44) (4) (0) (0)
Grade < a > b (c) Significant	Grade 1: Slight 2: Moderate 3: Marked 4: $(a > a : Number of animals examined at the siteb b: Number of animals with lesion(c) c: b / a * 100Significant difference ; *: P \leq 0.05 + *: P \leq 0.01 Test of Chi$	4 : Severe Chi Square			
(HPT150)					BATCA

(HPT150)

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : Al SEX : MALE

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

	Group Name No. of Animals on Grade	Control Study 50 1 2 3	100 ppm 50 2 3	200 ррш 50 2 3	400 ppm 50 2 3
Organ	Findings	(%) (%) (%)	(%) (%) (%)	(%) (%) (%)	(%) (%) (%) (%)
[Respiratory system]	system)				
nasal cavit	respiratory metaplasia:olfactory epithelium	<pre><50> 15 0 (0) (0) (30) (0) (0)</pre>	$\begin{array}{cccc} < 50 \\ 13 & 0 & 0 \\ (26) (0) (0) (0) \end{array}$	<pre><50> <16</pre>	<pre></pre>
	respiratory metaplasia;gland	50 0 0 0 0 (100) (48 0 0 0 0 (96) (0) (0)	50 0 0 0 0 0 (100)	49 0 0 0 0 0 0 (98) (0) (0) (0)
	squamous cell metaplasia:respiratory epithelium	2 0 0 0 (0) (0)	4 0 0 0 (8)(0)(0)(0)	20 0 0 0 ** (40)(0)(0)(0)	37 1 0 0 ** (74)(2)(0)(0)
	hyperplasia:transitional epithelium	(0)(0)(0) 0 0 0 0 0 0)(0)	(0)(0)(0)(0) (0)(0)(0)	(0)(0)(0)(0) 0 0 0 0 0	7 0 0 0 0 0 *
	atrophy:olfactory epithelium	(0)(0)(0)(0) 00000000000000000000000000	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{pmatrix}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	21 0 0 0 ** (42) (0) (0) (0)
nasopharynx	inflammation	<pre> <50> <50> (0) (0) (0)</pre> (0) (0)	<pre><cov 0 0 0 0 0 (0) (0) (0)</cov </pre>	$\begin{array}{cccc} <50 \\ 2 & 0 & 0 \\ (4) & (0) & (0) & (0) \end{array}$	<pre></pre>
larynx	inflammation	$\begin{array}{cccc} <50> & \\ 1 & 0 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$	$\begin{array}{cccc} <50 \\ & (50) \\ & 1 & 0 & 0 \\ & (2) & (0) & (0) \\ \end{array}$	<pre><50> </pre> <pre><50> </pre> 0 0 0 0 0 <pre></pre>	<pre><cov 3 0 (0) (0) (6) (0) (0)</cov </pre>
Grade < a > b (c)	<pre>1: Slight 2: Moderate 3: Marked a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100</pre>	4 : Severe			

(HPT150)

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : Al SEX : MALE

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

	Group Name No. of Animals on Study Grada	Control 50	100 ppm 50 ^	200 ppm 50	400 ppm 50
Organ	. Findings	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\frac{1}{(\%)} \frac{2}{(\%)} \frac{3}{(\%)} \frac{4}{(\%)}$	$\frac{1}{(\%)} \frac{2}{(\%)} \frac{3}{(\%)} \frac{4}{(\%)}$	$\frac{1}{(\%)} \frac{2}{(\%)} \frac{3}{(\%)} \frac{4}{(\%)}$
(Respiratory system)	y system)				
larynx	inflammation:foreign body	<pre><50> </pre> (0) (0) (0) (0)	<pre> <50> 2 0 0 (4) (0) (0) (0)</pre>	<pre><50> <10)(0)(0)</pre> <pre><100</pre> <pre><100</pre> <pre><100</pre> <pre><100</pre> <pre></pre>	<pre></pre>
lung	hemorrhage	<pre><60></pre> (0) (0) (0) (0)	<pre><cov 0 0 0 0 0 (0) (0) (0)</cov </pre>	<pre></pre>	$\begin{array}{cccc} <50 \\ & <50 \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{array}$
	edenza	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2 0 0 0 (4)(0)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
۶	inflammatory infiltration	6 2 0 0 (12)(4)(0)(0)	3 2 0 0 (6)(4)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	5 0 0 0 0 (0)
	fibrosis:focal	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ 2 & (& 0) & (& 0) & (& 0) \end{pmatrix}$	(0)(0)(0)(0) 0 (0)(0)	0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0) 000000
	accumulation of foamy cells	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 0 0 0 (0) (0)	1 0 0 0 (2)(0)(0)(0)	2 0 0 0 (0)
	bronchiolar—alveolar cell hyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1 1 0 0 (2)(2)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 3 0 0 (0) (6) (0) (0)
	inflammation:foreign body	(0)(0)(0)(0) 0 0 0 0	0 0 1 0 (0) (0) (2) (0)	1 0 0 0 (2)(0)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Grade < a > b	<pre>1 : Slight 2 : Moderate 3 : Marked a : Number of animals examined at the site b : Number of animals with lesion</pre>	4 : Severe			

(HPT150)

STUDY NO. : 0675 ANIMAL : RAT F344/DuCrICrlj[F344/DuCrj] REPORT TYPE : Al SEX : MALE

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

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		2 20 C	itrol 3 4	100 ppm 50 2 3	200 ppm 50 3	400 ppm 50 3	_ 、
Organ	Findings	(%) (%) (%)	(%) (%)	(%) (%) (%) (%) (%)	$\frac{1}{100} \frac{1}{100} \frac{1}$	1 2 3 (%) (%) (%)	4 (%)
(Hematopoietic system)	ic system}						
bone marrow	congestion	<pre><50></pre>	(0) 0) 0)	<pre><50> (0) (0) (0) (0) </pre>	<pre> <50> <50> (50) (50) (50) (50) (50) (50) (50) (50)</pre>	<pre><50> 1 0 0 (2) (0) (0) (</pre>	0 0
	deposit of hemosiderin	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) (0) 0 0 0 0	0 0
	granulation	0) (0) (0) 0 · 0 0	0) (0 0 0	(0)(0)(0)(0) 0 0 0 0 0	(0)(0)(0) 0 (0)(0)	1 0 0 (2)(0)(0)(0 0
	increased hematopoiesis	6 0 0 (12)(0)(0	(0) 0000	6 0 0 0 (12) (0) (0) (0)	5 0 0 0 0 (0)	8 0 0 (16)(0)(0)(0 0
	decreased hematopoiesis		0) 0 0	$\begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & (2) & (0) & (0) \end{pmatrix}$	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0) (0) (0) 0 0 0 0	0 0
spleen	congestion	<50> 0 0) ((0) (0 0 0	<pre>< 0) (0) (0)</pre> <pre></pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0)	<pre><50> <1 0 0 </pre>	0 0
	fatty change	$\begin{array}{cccc} 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$	0) ((0)(0)(0)(0) 0 (0)(0)) (0) (0) (0) 0 0 0 0	0 0
	deposit of hemosiderin	1 0 0 (2) (0) (0)	0 (0		(0)(0)(0)(0) 0 0 0 0	0 1 0 (0) (2) (0) (0 0
Grade < a > b	1 : Slight 2 : Moderate 3 : N a : Number of animals examined at the site	3 : Marked 4 : Severe site					1

(HPT150)

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STUDY NO. : 0675 ANIMAL : RAT F344/DuCrICrIj[F344/DuCrj] REPORT TYPE : A1 SEX : MALE

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

REPORT TYPE : A1 SEX : MALE					PAGE : 5
Organ Findings.	Group Name No. of Animals on Study Grade (%)	on Study 50 (%) (%) (%) (%)	$\begin{array}{cccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 3 4 (%) (%) (%) (%)
(Hematopoietic system)					
spleen fibrosis:focal		$\begin{array}{cccc} < 50 \\ 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{array}$	<pre><cov 0 0 0 0 0 0 0 0 0 0</cov </pre>	<pre><50></pre>	<pre><50> 1 0 0 (2) (0) (0)</pre>
extramedullary hematopoiesis		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 2 2 0 (6)(4)(4)(0)	3 3 2 0 (6)(6)(4)(0)	9 3 3 0 (18) (6) (6) (0)
lymph-follicular hyperplasia				$\begin{pmatrix} 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \\ \end{pmatrix}$	0 0 0 0 0 0 0 0 0
{Circulatory system}					
heart thrombus		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<pre></pre>	<pre><code <<="" <code="" td=""><td><pre></pre></td></code></pre>	<pre></pre>
myocardial fibrosis		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8 0 0 0 0 (0) (0) (0)	13 0 0 0 (26) (0) (0) (0)
(Digestive system)					
stomach ulcer:forestomach		<pre><50> 2 2 1 0 (4) (4) (2) (0)</pre>	<pre><50> 1 1 3 0 (2) (2) (6) (0)</pre>	<pre> <50> <50> (0) (0) (2) (0) (2) (0) (2) (0) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2</pre>	<pre><50> (50) (2)(0)(0)(0)</pre>
Grade 1: Slight 2: Moderate 3:) <a> a: Number of animals examined at the site b b: Number of animals with lesion (c) c: b/a * 100 (c) c: b/a * 100 Significant difference; *: P ≤ 0.05 **: P ≤ 0.	3 : Marked 4 : ; site ≦ 0.01 Test of Chi	4 : Severe f Chi Square			

(HPT150)

STUDY NO.	••	0675
ANIMAL	••	: RAT F344/DuCrlCrlj[F344/DuCrj]
REPORT TYPE	••	: Al
CEV	٠	

0rgan	Findings	Group Name Co No. of Animals on Study 50 Grade <u>1</u> 2((%) (%) ()	Control 50 3 4 % (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) opm	₽ 4 (%)
(Digestive system)	system)						
stomach	hyperplasia:forestomach	(50) (50) (2) (4) (0) (0 0 0	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>	$\begin{array}{cccc} < 50 \\ & (50) \\ 1 & 2 & 0 \\ (& 2) & (& 4) & (& 0) & (& 0) \end{array}$	<pre><code <="" <code="" code="" tr=""></code></pre>	0 0
	erosion:glandular stomach	3 1 (6)(2)(0) 0 0	3 0 0 0 (6)(0)(0)(0)	1 0 0 0 (2)(0)(0)(0)	4 0 0 (8)(0)(0)(0 0
	ulcer:glandular stomach	1 0 (2) (0) ((0) (0	(0)(0)(0)(0) 0 0 0 0 0 0 0	1 0 0 0 (2)(0)(0)(0)	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0
	hyperplasia:glandular stomach		(0) (0	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0) 0 0 0 0 0 (0)) (0) (0) 0 0 0 0	0 0
	mineralization:glandular stomach	$\begin{pmatrix} 1 & 0 \\ 2 \end{pmatrix} (2) (0) (-)$	0) (0 0 0		(0)(0)(0) 0 (0)(0)) (0) (0) (0) 0 0 0 0	0 ô
liver	herniation	<pre> 4 0 (8) (0) (1 </pre>	(0) 0 0	$\begin{array}{cccc} <50> & <50 \\ 7 & 0 & 0 & 0 \\ (14) & (0) & (0) & (0) \end{array}$	<pre><50> 6 0 0 0 (12) (0) (0) (0)</pre>	<pre><50> 12 0 0 (24) (0) (0) (</pre>	0 0
	necrosis:central	$\begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}$	0) 0 0	$\begin{pmatrix} 0 & 1 & 1 & 0 \\ (& 0) & (& 2) & (& 2) & (& 0) \end{pmatrix}$	0 1 0 0 (0)(2)(0)(0)	0 1 1 (0) (2) (2) (0 0
	fatty change:peripheral		(0) (0	0 1 0 0 (0) (2) (0) (0)	(0)(0)(0)(0) 0 0 0 0	0 1 0 (0) (2) (0) (0 0
Grade < a > b	1 : Slight 2 : Moderate 3 : N a : Number of animals examined at the site h : Number of animals with Inviou	3 : Marked 4 : Severe site					

STUDY NO. : 0675 ANTMAL : RAT F344/DuCrlCrlj[F344/DuCrj] REPORT TYPE : Al SEX : MALE

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

Organ	Group Name No. of Animals on Grade Findings	e Control imals on Study 50 (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
{Digestive system}	(stem)				
liver	granulation	$\begin{array}{cccc} < 50 \\ 37 & 1 & 0 & 0 \\ (74) & (2) & (0) & (0) \\ \end{array}$	$\begin{array}{cccc} <50 \\ 41 & 0 & 0 \\ (82) & (0) & (0) \\ \end{array}$	<pre> <50> <50> </pre> <2 0 0 (0) (0) (0) (0)	<pre><50> 33 0 0 0 (66) (0) (0) (0)</pre>
	increased extramedullary hematopoiesis	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{pmatrix}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0)(0) 0 0 0 0 0	(0)(0)(0)(0) 00000000000000000000000000
	clear cell focus	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	3 1 1 0 (6)(2)(2)(0)	3 1 0 0 (6)(2)(0)(0)
	acidophilic cell focus	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7 5 0 0 (14)(10)(0)(0)	6 4 1 0 (12)(8)(2)(0)
	basophilic cell focus	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 1 0 0 (6)(2)(0)(0)	6 2 0 0 (12)(4)(0)(0)
	spongiosis hepatis	5 0 0 0 (10) (0) (0) (0)	7 0 0 0 0 0 (0) (0)	3 0 0 0 (0) (0)	3 0 0 0 0 (0)
	bile duct hyperplasia	6 44 0 0 (12)(88)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 40 0 0 (18) (80) (0) (0)	10 38 0 0 (20)(76)(0)(0)
pancreas	atrophy	(50) (50) (50) (50) (50) (50) (50) (50)	$\begin{array}{ccc} <50 \\ 7 & 1 & 0 & 0 \\ (14) & (2) & (0) & (0) \end{array}$	$\begin{array}{ccc} <50> \\ 7 & 1 & 0 \\ (14) & (2) & (0) & (0) \end{array}$	$\begin{array}{cccc} <50> \\ 7 & 0 & 0 \\ (14) & (0) & (0) \\ \end{array}$
Grade < a > b	<pre>1 : Slight 2 : Moderate 3 : Marked a : Number of animals examined at the site b : Number of animals with lesion</pre>	4 : Severe			

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(HPT150)

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0675	RAT F344/DuCr1Cr1,[F344/DuCr1]	ll second	MALE	
-	_		-	
•••	•••	••	••	
STUDY NO.	ANTMAL.	REPORT TYPE : A1	SEX	

			randania produkta produkta produkta		
OrganFindings	Group Name No. of Animals on Study Grade		100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
(Digestive system)					
pancreas islet cell hyperplasia		$\begin{array}{cccc} <50> & \\ 4 & 2 & 0 & 0 \\ (8) & (4) & (0) & (0) \end{array}$	<pre><50> 3 0 0 0 (6) (0) (0)</pre>	$\begin{array}{cccc} <50 \\ 1 & 0 & 0 \\ (2) (0) (0) (0) \end{array}$	<pre> <50> <50> (0) (0) (0)</pre>
{Urinary system}					
kidney necrosis:focal		<pre><50> (50) (50) (50) (50) (50) (50) (50) (50)</pre>	$\begin{array}{cccc} <50 \\ 1 & 0 & 0 \\ (2) & (0) & (0) \\ \end{array} \right)$	<pre><cov 0 0 0 0 0 (0) (0) (0)</cov </pre>	<pre> <50> <50> <50> (0) (0) (0) (0)</pre>
hyaline droplet		3 0 0 0 0 (0) (0)	(0) (0) (0) (0) 0 0 0 (0)	0 1 0 0 (0)(2)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
chronic nephropathy		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	17 22 7 2 (34) (44) (14) (4)	5 10)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
mineralization:cortex		$\begin{pmatrix} 1 & 0 & 0 & 0 \\ 2 & (& 0) & (& 0) & (& 0) \end{pmatrix}$	0 0 0 0 0 0 0 (0)	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0) (0) (0) 0 0
urothelial hyperplasia:pelvis	lvis	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ 2 & (& 0) & (& 0) & (& 0) \end{pmatrix}$) (0 0)	1 0 0 0 (2)(0)(0)(0)	(0) (0) (0) (0) 0 0 0 (0)
urin bladd dilatation		$\begin{array}{cccc} & <50 \\ & 1 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre><50> (0) (0) (0) (0) </pre>	$\begin{array}{cccc} <50 \\ 2 & 0 & 0 \\ (4) & (0) & (0) & (0) \end{array}$	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>
Grade 1 : Slight 2 : Moderate < a > a : Number of animals examined at the b b : Number of animals with Iseion	ate 3 : Marked ned at the site . Teaion	4 : Severe			

(HPT150)

STUDY NO. ANIMAL REPORT TYPE		H	LL ANTMALS (0-1054)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		
VIC	ALIAN .					PAGE : 9
Organ	Findings	Group Name No. of Animals on Study Grade	Control tudy 50 3 4 (%) (%) (%) (%)	$\begin{array}{ccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
{Urinary system} urin bladd	stem) papillomatosis		<pre></pre>	<pre><code <="" pre=""></code></pre>	<pre><pre><60></pre> <pre><60></pre> <pre><60></pre> <pre></pre> <</pre>	(0)(0)(0) (0)(0)(0) (0)(0)(0)(0)(0)(0)(0)(0)(0)(0)(0)(0)(0)(
{Endocrine system}	system)					
pituitary	angiectasis		<pre><50> <!--50--> </pre> (0) (0) (0) (0)	<pre><50></pre>	<pre><0></pre> <pre><0></pre> <pre><0</pre> <pre></pre> <pre><0</pre> <pre></pre> <pre><</pre>	<pre></pre>
	cyst		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2 0 0 0 (4)(0)(0)(0)	(0)(0)(0)(0) 0 0 0 0
	hyperplasia		18 5 0 0 (36)(10)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8 5 3 0 (16)(10)(6)(0)	19 2 1 0 (38) (4) (2) (0)
	Rathke pouch		2 0 0 0 (0) (0)	6 0 0 0 (12)(0)(0)(0)	4 0 0 0 (8)(0)(0)(0)	3 0 0 0 (6)(0)(0)(0)
thyroid	follicular hyperplasia		<pre><50> <1 0 0 </pre> (2) (0) (0) (0)	<pre><50> 2 0 0 (4) (0) (0) (0)</pre>	<pre><50></pre> <pre><50></pre> (0) (0) (0) <pre>(0)</pre>	<pre><50></pre>
Grade < a > b (c) Significant (HPT150)	Grade 1 : Slight 2 : Moderate < a > a : Number of animals examined at the b b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P ≤ 0.05 ** : P (HPT150)	3 : Marked 4 site ≦ 0.01 Test of C	: Severe ini Square			
/						BAIS4

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STUDY NO: ANIMAL .: REPORT TYPE :: SEX .:	: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : A1 : MALE	ULA ALL	HISTOPATHOLOCICAL FINDINGS :1 ALL ANTMALS (0-105W)	L ANTMALS (0-105W)		PAGE :	10
Organ	Findings	Group Name No. of Animals on Study Grade	y Control y 50 (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 ppm (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)	
(Endocrine system)	ystem)						
thyroid	C-cell hyperplasia	5	<pre><50> 8 1 2 0 (16) (2) (4) (0)</pre>	$\begin{array}{cccc} <50 \\ 12 & 3 & 1 & 0 \\ (24) & (6) & (2) & (0) \end{array}$	$\begin{array}{cccc} <50> \\ 12 & 0 & 1 & 0 \\ (24) & (0) & (2) & (0) \end{array}$	<pre><50> 6 3 1 0 (12) (6) (2) (0)</pre>	
	cystic thyroid follicle	Ŭ	(0) (0) (0) (0) (0)	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0)(0) 0 0 0 0	(0)(0)(0) 0000)	
parathyroid	hyperplasia	Č	<pre> <50> <50> (50) (0) (10) (0) (0) (0) (0) (0) (0) (0) (0) (0) (</pre>	<pre><50> (0) (0) (0) (0) (0)</pre>	<pre><50> (0) (0) (0) (0) </pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0) (0)	
adrenal	thrombus .		<pre> <50> (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)</pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0)	<pre>< 0) (0) (0) (0)</pre>	<pre> <50> <50> (50) (50) (50) (50) (50) (50) (50) (50)</pre>	
	cyst	C	(0) (0) (0) (0) (0)	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0)(0) 0 0 0 0	(0)(0)(0)(0) 000000	
	hyperplasia:cortical cell	J	(0) (0) (0) (0) (0)	2 0 0 0 (4)(0)(0)(0)	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0)(0) 00000000000000000000000000	
	hyperplasia:medulla	J	3 3 0 0 6) (6) (0) (0)	2 3 0 0 (4)(6)(0)(0)	0 4 1 0 (0) (8) (2) (0)	0 2 2 0 (0) (4) (4) (0)	
Grade 1 : Slight < a > a : Number b b : Number b c : b / a * (c) c : b / a *	2 : Moderate of animals examined of animals with lesi • 100 ★ : P ≤ 0.05	Aarked 4:5 01 Test of Chi	Severe Square				1

BAIS4

(HPT150)

0675	RAT F344/DuCrlCrlj[F344/DuCrj]	: Al	MALE	
	••		•••	
STUDY NO.	ANIMAL	REPORT TYPE :	SEX	

Organ	Findings	Group Name No. of Animals on Study Grade <u>1</u> (%	dy Control 1 2 3 4 (%) (%) (%) (%)	$\begin{array}{cccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
(Endocrine system)	ystem)					
adrenal	focal fatty change:cortex	J	3 0 0) (0) (0) 3 0 0 0 6) (0) (0)	<pre><50> 1 0 0 (2) (0) (0)</pre>	<pre><50> 3 0 0 (6) (0) (0) </pre>	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>
(Reproductive system)	e system)					
testis	mineralization		<pre><50> 1 0 0 0 2) (0) (0) (0)</pre>	<pre> <50> < 0 (0) (0) (0)</pre>	<pre> <50></pre>	<pre><50> <pre><50> <pre>(5)(0)(0)</pre></pre></pre>
	interstitial cell hyperplasia	J	3 0 0 0 6) (0) (0) (0)	$\begin{pmatrix} 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{pmatrix}$	6 0 0 0 (12)(0)(0)(0)	2 0 0 0 (4)(0)(0)(0)
semin ves	inflammation		<pre><50></pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0)	<pre><50> </pre> <pre><50> </pre> (0)(0)(0)(0)	<pre></pre>
	hyperplasia		0 0 1 0 0) (0) (2) (0)	(0)(0)(0)(0) 0 0 0 0 0 0)		(0)(0)(0) (0)(0)(0)
prostate	inflammation		<pre> <50> <50> (18) (6) (0) (0)</pre>	$\begin{array}{cccc} <50> \\ 10 & 1 & 0 & 0 \\ (20) & (2) & (0) & (0) \end{array}$	<pre><50> 7 0 0 0 (14) (0) (0) (0)</pre>	$\begin{array}{ccc} & \langle 50 \rangle \\ & 5 & 1 & 1 & 0 \\ (10) & (& 2) & (& 2) & (& 0) \end{array}$
Grade < a > b (c)	Grade 1 : Slight 2 : Moderate 3 :) < a > a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b / a * 100	Marked 4:	: Severe			

STUDY NO.	••	0675
ANIMAL	••	: RAT F344/DuCrlCrlj[F344/DuCri]
REPORT TYPE : A1	••	Al
SEX	••	: WALF

Group No. of OrganFindingsGrade	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
(Reproductive system)				
prostate hyperplasia	$\begin{array}{cccc} <50> \\ 10 & 0 & 0 \\ (20) & (0) & (0) \\ \end{array}$	<pre><50> 9 0 0 (18) (0) (0) (0)</pre>	$\begin{array}{cccc} & <50 \\ 11 & 3 & 0 & 0 \\ (22) & (6) & (0) & (0) \end{array}$	<pre> <50> <50> (10) (0) (0) (0)</pre>
(Nervous system)				
spinal cord gliosis	$\begin{pmatrix} <50 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} <0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} <0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} <0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} <0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 $	$\begin{array}{cccc} < 50 \\ 1 & 0 & 0 \\ (2) & (0) & (0) \\ \end{array} $	<pre><code <<="" <code="" td=""><td><pre><60> </pre> <pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre></td></code></pre>	<pre><60> </pre> <pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>
{Special sense organs/appendage}				
eye cataract	$\begin{array}{cccc} <50> \\ 1 & 2 & 0 & 0 \\ (& 2) & (& 4) & (& 0) & (& 0) \end{array}$	$\begin{array}{cccc} <50 \\ & (50) \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{array} $	<pre><50> 2 0 0 (4) (0) (0) (0)</pre>	<pre><50> </pre> <pre><50> </pre> <pre>(0) (0) (0) (0)</pre>
retinal atrophy	1 0 3 0 (2)(0)(6)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 0 2 0 (0) (0) (4) (0)	(0)(0)(0)(0) 0 0 0 0
keratitis	3 0 0 0 (6)(0)(0)(0)	(0)(0)(0) 0 (0)(0)	(0)(0)(0)(0) 0 0 0 0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Grade 1 : Slight 2 : Moderate 3 : Marked < a > a : Number of animals examined at the site b b : Number of animals with lesion	rked 4 : Severe			

(HPT150)

BAIS4

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STUDY NO. : 067 ANIMAL : RAT REPORT TYPE : A1 SEX : MAL	: 0675 : RAT F344/buCrlCrlj[F344/buCrj] : Al : MALE	HISTOPATHOLOGICAL FINDINGS :N ALL ANTWALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)		PAGE : 13
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	200 ppm 50 (%) (%) (%) (%)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
(Special se	(Special sense organs/appendage)				
өуө	iritis	$\begin{array}{cccc} & <50 \\ & & \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0)	<pre><50> </pre> <pre><50> </pre> (0) (0) (0) (0)	<pre><50> </pre> <pre><50> </pre> <pre>(0) (0) (0)</pre>
	ulcer:cornea	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ 2 & (& 0) & (& 0) & (& 0) \end{pmatrix}$	(0)(0)(0) 0 (0)(0)	(0)(0)(0)(0) 0 0 0 0 0 0)(0)	0 1 0 0 (0) (2) (0) (0)
Harder gl	inflammation	<pre><50> 3 0 0 0 (6) (0) (0)</pre>	<pre><50> (2) (0) (0) (0)</pre>	$\begin{array}{cccc} <50 \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>
	epidermal cyst	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{pmatrix}$	(0)(0)(0) 0 0 0 0 0 0)	(0)(0)(0)(0) 00000000000000000000000000	(0)(0)(0)(0) 00000000000000000000000000
[Musculoske]	(Musculoskeletal system)				
bone	dysplasia	$\begin{pmatrix} & 0 \\ & $	$\begin{pmatrix} < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 0 \\ < 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><50> 0 1 0 0 (0) (2) (0) (0)</pre>	<pre><50> </pre> <pre><50> </pre> <pre><50> </pre> <pre></pre> <pr< td=""></pr<>
	osteosclerosis	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0)(0) 00000000000000000000000000	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
Grade < a > b (c) Significant	Grade 1 : Slight 2 : Moderate 3 :) (a > a : Number of animals examined at the site b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P ≤ 0.05 ** : P ≤ 0.05	3 : Marked 4 : Severe ∋ site ≥ ≦ 0.01 Test of Chi Square			
(HPT150)					BAIS4

TABLE L4

All Marine

10000

HISTOPATHOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS : FEMALE ALL ANIMALS

92

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STUDY NO.	••	0675
ANIMAL	••	: RAT F344/DuCr1Cr1i[F344/DuCri]
REPORT TYPE : A1	••	IV IV
SEX	٠	FEWAL F

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $							
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Group No. o	•	വാ	200 ppm 50	400 F	nd
	Ju		2 3 (%) (%)	2 3 (%) (%)	2 3 (%) (%)		4 (%)
	tegumentary :	system/appandage)					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	u∕ app	inflammation	<50> 0 0 0) (0) (<pre><50> 0 (0) (0</pre>		0 (0) (0 (O)
$ \label{eq:restrict} y \mbox{ system} \\ adhesion \\ adhesion \\ throubus \\ throubus \\ throubus \\ mineralization \\ estinophilic charge:offectory epithelium \\ \end{tabular} \end{tabular}$	outis	abscess	<pre> <50> 0</pre>	<pre><50> 0 1 0 0) (2) (0) (</pre>	<pre>< <50></pre>	0 (0) (0 (O)
$ \begin{array}{ccccccccc} \mbox{adhesion} & (50) & (50$	spiratory sy:	stem)					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	al cavit	adhesion	<pre><code (c)="" (c)<="" color="" td=""><td><pre>< <50></pre></td><td><pre><50> (0) ((0) (</pre></td><td><pre><50> 0 0 (0) (0)</pre></td><td>0 (0)</td></code></pre>	<pre>< <50></pre>	<pre><50> (0) ((0) (</pre>	<pre><50> 0 0 (0) (0)</pre>	0 (0)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		thrombus	2 0 0 4) (0) (0) (3 0 0 6) (0) (0) () (0) (0) (0 0 0 0 0	$\begin{pmatrix} 0 &) & (0 &) \\ 0 & 0 & 0 \end{pmatrix}$	0 0)
13 35 2 0 16 33 1 0 18 30 0 37 8 0 (26) (70) (4) (0) (32) (66) (2) (0) (36) (60) (0) (74) (16) (0)		mineralization) (0) (0) 0 0	28 0 0 56) (0) (0) () (0) (0) 0 0	0) (0 0 0	0 0)
		eosinophilic change:olfactory epithelium	35 2 70) (4) (1 (2)() 0 (0	8 0 (16) (0)	# (0)

(HPT150)

PAGE : 15

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 48 0 0 00 45 1 0 (90) (2) (0) (100 ppm 2 3 (%) (%) 3 0 0 (6)(0)(0)(27 0 0 (54) (0) (0) (2 1 0 (4)(2)(0)(20 <50> -8
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 00 4 (% 00 200 ppm 50 2 3 (%) (%) (9 3 1 0 (6)(2)(0)(49 0 0 (98) (0) (0) (<50> - 8 HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) 4 8 00 00 00 100 ppm 50 2 3 (%) (%) (() (0) (0) (0) 0 0 0 0 9 0 0 (18) (0) (0) (5 0 0 (10) (0) (0) (50 0 0 0 (100) (0) (<50> - 8 4

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 5 0 0 0 0 (10) (0) (0) 1 0 0 0 (2)(0)(0)(0) 48 0 0 0 0 (96) (0) (0) (0) Control 2 3 (%) (%) 50 <50> -18 Group Name No. of Animals on Study Grade <u>1</u> respiratory metaplasia:olfactory epithelium eosínophilic change:respiratory epithelium inflammation:respiratory epithelium STUDY NO. : 0675 ANTMAL : RAT F344/Ducrlcrlj[F344/Ducrj] REPORT TYPE : Al SEX : FEMALE respiratory metaplasia:gland inflammation:foreign body Findings. {Respiratory system} nasal cavit Organ_

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

39 4 0 0 ** (78) (8) (0) (0)

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6 0 0 (12) (0) (0) (

5 0 0 0 (10) (10) (10) (10)

squamous cell metaplasia:respiratory epithelium

desquamation:olfactory epithelium

hyperplasia:transitional epithelium

) 0 0

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- - -0 0

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

4 : Severe

3 : Marked

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

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

BAIS4

(HPT150)

0675	RAT F344/DuCrlCrlj[F344/DuCrj]	: AI	FEMALE	
•••	••		•••	
STUDY NO.	ANIMAL	REPORT TYPE	SEX	

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Organ	Findings	Group Name No. of Animals on Study Grade <u>1</u> (%	Control 50 2 3) (%) (%)	(%)	1 2 (%) (%)	100 ppm 50 2 3 4 (%) (%) (%)		1 2 (%) (%)	200 ppm 50 201 ppm 2 3 4 6) (%) (9	on (%)	<u>1</u> (%)	2 (%)	400 ppm 50 2 3 4 %) (%) (9	ц (%)
(Respiratory system)	ystem)								- - - -					
nasal cavit	atrophy:olfactory epithelium		<pre></pre>	0 (0	(0) (0) (<pre><50> (50) (0) (0) (0) (0) (0) (0) (0) (0) (0) (</pre>	Ŭ	2) (0) (<pre></pre>	0	20 (40)	<pre><60></pre>	0 0 0	** () 0
larynx	inflammation		<pre>< 50></pre> <pre> (18) (0) (0) (</pre>	0 0	<pre><50> 14 0 (28) (0) (</pre>	<pre><50> (50) (0) (0) (0) (0) (0) (0) (0) (0) (0) (</pre>		11 0 (22) (0)	<pre><20></pre>	0 0	7 (14)	<pre>(0) (</pre>	0 0 0	0 0
	inflammation:foreign body		2 0 0 (4)(0)(0)(0 0	1 0 (2)(0)	(0)(0) 000	÷	2 0 4) (0)) (0) 0)	0 0	0 0) 0)) 0	0 0
lung	hemorrhage		<pre><50></pre> <pre><50></pre> (0)(0)(0)(0 (0	<pre></pre>	<50> 0 0 0 0) (0) (0)	-	0) (0 0) (0	<pre><50> 0 (0) (0</pre>	0 0	1 (2)	<pre><60></pre>	(50) (0 (0 0
	edema		4 0 0 (8)(0)(0)(0 0	2 0 (4)(0)	(0) (0)	-	1 0 2) (0)) (0 0		1 (2)) (0 0) 0	0 0
	inflammatory infiltration		4 0 0 (8)(0)(0)(0 0	4 0 (8)(0)	(0)(0) 000	÷	0) (0 0) (0) 0)	0 0	1 (2)) (0 0) 0 (0	0 0
	accumulation of foamy cells		2 0 0 (4)(0)(0)(0 (0	2 0 (4)(0)	(0) (0) 0 0	Ŭ	3 0 6) (0)) (0)	0 0	1 (2)) (0 0)) 0	0 0
Grade < a > b 1 (c)	<pre>1 : Slight 2 : Moderate 3 :] a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100</pre>	3 : Marked • site	4 : Severe											

: 0675	: RAT F344/DuCrlCrlj[F344/DuCrj]	: A1
		ЪЕ
		Д,

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ANIMAL REPORT TYPE SEX	: RAT F344/DuCrlCrlj[F344/DuCrj] : Al : FEMALE	ALL ANTMALS (0-105W)	ALL ANTMALS (0-105#)				PAGE :
Organ	Findings	Group Name No. of Animals on Study Grade 1 (%)	Control 50 (%) (%) (%)	$\begin{array}{cccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \\ \end{array}$	200 ppm 50 (%) (%) (%) (%)	5 (%) (%)	400 ppm 50 3 4 (%) (%)
(Respiratory system) lung bron	y system) bronchiolar-alveolar cell hyperplasia	a (4) (4)	<pre><50> <1 0 0 </pre>	$\begin{array}{cccc} & <50 \\ & & <50 \\ & & 1 \\ & & 0 \\ & & & 1 \\ & & & 0 \\ & & & & 0 \end{array}$	<pre></pre>	3 (5 (6) (0)	<pre><code color="1"></code></pre>
lema topoie1	(Hematopoietic system)						
bone marrow	deposit of hemosiderin	0 (0)	<pre><50> </pre> < 60> (0) (0) (0)	<pre> <50> < 0) (0) (0)</pre>	<pre></pre>	<pre></pre>	<pre><50> 0 0 (0) (0)</pre>
	granulation	0 0	1 0 0 (2)(0)(0)	2 0 0 0 (4)(0)(0)(0)	(0)(0)(0) 0 (0)(0)	1 0 (2)(0)	(0)(0) 000
	increased hematopoiesis	9 (18)	(0)(0)(0) 000	6 0 0 0 (12)(0)(0)(0)	3 0 0 0 0 (0) (0)	5 0 (10) (0)	(0)(0) 000
	myelofibrosis	0 (0)	(0)(0)(0) 000	0 1 0 0 (0) (2) (0) (0)	(0)(0)(0) (0)(0)(0)	(0)(0) 00)	(0)(0) 000
spleen	congestion	1 (2)	<pre><60></pre> <pre><60></pre> <pre></pre> <pre><td><pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre></td><td><pre> <50> < 50> (0) (0) (0)</pre></td><td>(0) (0) (0 0 <50></td><td><pre><50> (50) (0) (0) (0)</pre></td></pre>	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>	<pre> <50> < 50> (0) (0) (0)</pre>	(0) (0) (0 0 <50>	<pre><50> (50) (0) (0) (0)</pre>
Grade < a > b	 Slight 2 : Moderate 3 Number of animals examined at the s Number of animals with lesion 	3 : Marked 4 : Severe site					

(HPT150)

0675	RAT F344/DuCrlCrlj[F344/DuCrj]	Al	FEMALE	
••	•••		••	
STUDY NO.	ANTMAL	REPORT TYPE	SEX	

	Group Name No. of Anii	lame Control Animals on Study 50	100 ppm 50	200 ppm 50	400 ppm 50
Organ	Grade Findings	Grade <u>1 2 3 4</u> (%) (%) (%) (%)	$\frac{1}{(\%)} \begin{array}{c} & & \\$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	00 (%) (%) (%) (%) (%)
lematopoie t	(Hematopoietic system)				
spleen	deposit of hemosiderin	$\begin{array}{cccc} <50> & \\ 11 & 0 & 0 & 0 \\ (22) & (0) & (0) & (0) \end{array}$	<pre><50> 7 0 0 0 (14) (0) (0) (0)</pre>	<pre><50> </pre> <pre><50> </pre> <pre>8 0 0 0 </pre> <pre>(16) (0) (0) (0)</pre>	<pre><50> <15 0 0 0 </pre>
	inflammation	(0)(0)(0)(0) 00000000000000000000000000	$\begin{pmatrix} 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{pmatrix}$	(0)(0)(0) 0 (0)(0)	(0)(0)(0)(0) 00000
	fibrosis:focal	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0) 0 (0)(0)	(0)(0)(0) (0)(0)(0)	(0)(0)(0)(0) 00000000000000000000000000
	extramedullary hematopoiesis	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	12 2 2 0 (24) (4) (4) (0)	18 1 0 0 (36)(2)(0)(0)	16 2 2 0 (32)(4)(4)(0)
{Circulatory system}	system}				
heart	thrombus	$\begin{array}{cccc} & <50 \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \\ \end{array}$	<pre><50> (50) (2) (0) (0) (0)</pre>	<pre><code <="" color="" pre=""></code></pre>	$\begin{array}{cccc} & \langle 50 \rangle \\ & 1 & 0 \\ & 2 \rangle & (& 0 \rangle & (& 0 \rangle \\ \end{array} $
	myocardial fibrosis	6 1 0 0 (12)(2)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7 0 0 0 0 (14) (0) (0) (0)	5 0 0 0 0 (0) (0) (0)
	arteritis	1 0 0 0 (2)(0)(0)(0)		0 0 0 0 0 0 0	(0)(0)(0)(0) 00000000000000000000000000
Grade < a > b (c)	<pre>1 : Slight 2 : Moderate 3 : Marked a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100</pre>	d 4 : Severe			

PAGE : 19 48 00 o 6 0 0 00 00 400 ppm 4 1 0 (8)(2)(0)(3 1 1 (6)(2)(2)(1 0 0 (2)(0)(0)(0 0 1 (0) (0) (2) (14 0 0 (28) (0) (0) (\cup 1 1 0 (2)(2)(0)(1 0 0 (2)(0)(0)(3 (%) 0 0 0 0 <50> 50 8 <50> 20 0 0 0 0) - 8 48 0 0 00 00 00 o 6 0 0 0 0 00 200 ррт 50) 0 (i) 1 0 1 (2)(0)(2)() 0 (0) (0) (0) (0) 0 0 0 0 1 0 0 (2)(0)(0)(1 0 0 2) (0) (0) (2 3 (%) (%)) (0) (0) (0 0 0 0 <20 <50> <50> (1 (2) (1 _ \cup 4 00 00 0 0 00 o 6 0 0 o 6 00 100 ppm
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 (2)
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 (6)
 (
 4 0 0 (8)(0)(0)() 0 (i)) 0 0) 0 0) (0) (0) (0) 0 0 0 0 7 0 0 (14) (0) (0) () (0) (0) (0) 2 3 (%) (%) 0) (0) 0 (0) 1 0 ((2)(0)(0 50 <20> $\begin{pmatrix} 1 & 1 \\ (2) & (2) \end{pmatrix}$ <20 <20 <u>(5</u>0 - 8 2 3 4 (%) (%) (%) (0)(0)(0)(0) 0 0 0 0 0 (0)(0)(0)(0)(0) 0000000 2 0 1 0 (4)(0)(2)(0) 0 0 o ô 1 0 0 0 0 (2) (0) (0) 7 0 0 0 0 (14) (0) (0) (0) Control 1 0 0 2) (0) (0) (1 0 0 (2)(0)(0)(50 <50> €00 <50> Test of Chi Square 4 : Severe - 8 Group Name No. of Animals on Study Grade 1 _ 3 : Marked : P ≦ 0.01 1 : Slight 2 : Moderate 3 : W a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100 mineralization:glandular stomach ¥ STUDY NO. : 0675 ANIMAL : RAT F344/DuCrlcrlj[F344/DuCrj] REPORT TYPE : A1 SEX : FEMALE erosion:glandular stomach squamous cell metaplasia ulcer:glandular stomach hyperplasia:forestomach ulcer:forestomach dilatation herniation Findings (Digestive system) large intes stomach Organ liver

(HPT150)

STUDY NO. ANIMAL REPORT TYPE SEX	: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : Al : FEMALE		HISTOPATHOLOCICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)	L FINDINGS :1 05W)	NON-NEOPLASTI	c Lesions (S	UMMARY)						king (PAGE :	20
Organ	Findings	Group Name No. of Animals on Study Grade	6 (%)	Control 3 4 (%) (%)	1 (%)	100 ррш 50 (%) (%) ((%)	1 (%)	200 50 (%) (%)	200 ppm 3 4 (%) (%)	(%) (%)	8	400 ppm 50 3 (%)	₽ (%)	
(Digestive system)	ystem)						- - -							-	
liver	peliosis-like lesion		<pre></pre>	0) (0 0 0	0 0	<pre><50> 0 (0) (</pre>	0 0	· 2 (4) (<50> 0 0 0 (0)	0)	0 0	0 0)	<pre><60> 0 (0) (</pre>	0 (0	
	necrosis:central		1 0 (2) (0) (0) 0) 0	0	$\begin{pmatrix} 1 & 0 \\ 2 \end{pmatrix} (0) (-)$	0) (0 0)	0) (0 0	0)	0 0	0)	0 0)	0 (0	
	necrosis:focal		2 0 (4)(0)(0) 0 0	1 (2)(0 (0	1 (2) ((0 0 (0 0	0 0 0	1 (2)	0 0)) 0)	0 0	
	fatty change:central) (0) (0) 0 0	0) (0 0 0	0	1 2 (2) (4) (0 (0) (0 0)	0) (0 0 0	0 (0)	0 0	0 (0)	1 (2)(0 0	
	fatty change:peripheral) (0) (0) 0 0	0) 0 0	0 0 0		0 (0) (0 0)	1 0 2) (0)	0)	0 0	0 0)) (0 0)	0 0	
	mineralization) (0) (0) 0 0	0) (0 0 0	0 0 0	0) (0 0 0	0 (0	1 (2) (0) (0 0	0 (0)	0 0)	0 0)) 0)	0 0	
	degeneration:central) (0) (0) 0 0	1 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	
	inflammatory infiltration) (0) (0) 0 0	0) (0 0 0	1 (2)(2)	$\begin{matrix} 1 & 0 & (\\ 2) & (& 0) & (& (\\ 0) & (& 0) \end{matrix}$	0 (0	1 (2)(0) 0 0	0 0	0)	0 0)) (0 0)	0 0	
Grade < a > b (c) Significant c	Grade 1 : Slight 2 : Moderate 3 :) < a > a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P ≤ 0.05 ** : P ≤ 0.	farked 01	4 : Severe Test of Chi Square												

SEX	: AI : FEMALE				PAGE :
Organ	Group Name No. of Anii Grade Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
(Digestive system)	, system)				
liver	lymphocytic infiltration	$\begin{pmatrix} <50 \\ 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \\ \end{pmatrix}$	$\begin{array}{ccc} < 50 \\ 0 & 1 & 0 \\ (& 0) & (& 2) & (& 0) \\ \end{array} $	<pre><50> </pre> <pre><50> </pre> 0 0 0 0 (0) (0) (0)	<pre><50> </pre> <pre><50> </pre> <pre>(0) (0) (0)</pre>
	granulation	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	19 6 1 0 (33)(12)(2)(0)	18 3 0 0 (36)(6)(0)(0)
	scar	0 0 0 0 0 0 0 0 0	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{pmatrix}$	(0)(0)(0)(0) 0 0 0 0 0 (0)	(0)(0)(0)(0) 0 0 0 0
	increased extramedullary hematopoiesis		0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		1 0 0 0 (2)(0)(0)(0)
	clear cell focus	(0)(0)(0) 0 (0)(0) 0 (0)	3 1 0 0 (6)(2)(0)(0)	3 0 0 0 0 (0) (0)	3 1 0 0 (6)(2)(0)(0)
	acidophilic cell focus	2 0 0 0 (4)(0)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0)(0) 0 0 0 0 0 0	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	basophilic cell focus	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9 2 0 0 (18) (4) (0) (0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	bile duct hyperplasia	6 0 0 0 (12)(0)(0)(0)	15 0 0 0 * (30) (0) (0) (0)	6 0 1 0 (12)(0)(2)(0)	5 0 0 0 0 (0)
Grade < a > b	<pre>1 : Slight 2 : Moderate 3 : Marked a : Number of animals examined at the site b : Number of animals with lesion</pre>	d 4:Severe			

BAIS4

(HPT150)

0675	RAT F344/DuCrlCrlj[F344/DuCrj]	Al	FEMALE	• •
•••	••	••	••	
STUDY NO.	ANTMAL	REPORT TYPE : A1	SEX	

		Name Control Animals on Study 50	100 ppm 50	2 50	400 ppm 50
Organ	6 Findings	Grade <u>1 2 3 4</u> (%) (%) (%) (%) (%)	$\frac{1}{(\%)} \frac{2}{(\%)} \frac{3}{(\%)} \frac{4}{(\%)}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \frac{1}{(\%)} \begin{array}{c} 2 & 3 & 4 \\ (\%) & (\%) & (\%) & (\%) \\ \end{array} $
{Digestive system}	/stem)				
pancreas	atrophy	<pre><50> 2 0 0 (4) (0) (0) (0)</pre>	<pre> <50> <50> (50) (50) (50) (50) (50) (50) (50) (50)</pre>	<pre><50> 6 0 0 0 (12) (0) (0) (0)</pre>	<pre><code color(color)<="" td=""></code></pre>
	islet cell hyperplasia		0 1 0 0 (0) (2) (0) (0)		$\begin{array}{cccccccccccccccccccccccccccccccccccc$
{Urinary system}	tem)				
kidney	necrosis:focal	<pre><50></pre>	<pre><50> 0 1 0 0 (0) (2) (0) (0)</pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0)	<pre><code color(color)<="" td=""></code></pre>
	hyaline droplet	(0)(0)(0) 0(0)(0) 0(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{pmatrix} 1 & 0 & 0 & 0 \\ (2) & 0) & (0) & (0) \end{pmatrix}$	(0)(0)(0)(0) 0 0 0 0
	chronic nephropathy	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	18 7 3 0 (36)(14)(6)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	15 9 0 1 (30)(18)(0)(2)
	mineralization:cortex	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)
	urothelial hyperplasia:pelvis	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0)(0) 0 0 0 0	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(0)(0)(0)(0) 0 0 0 0 0 0 0
Grade 6 a > b (c) Significant d	Grade 1 : Slight 2 : Moderate 3 :) < a > a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b / a * 100 Sciniticant difference + 0 < 0 < 10 < 10 < 0 < 0 < 0 < 0 < 0 < 0	3 : Marked 4 : Severe site			

STUDY NO. : 0675 ANIMAL : RAT REPORT TYPE : A1 SEX : FEMA	: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : Al : FEMALE	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	² C	PAGE : 23
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%) (%)	$\begin{array}{cccc} 100 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{ccc} 400 \text{ ppm} \\ 50 \\ (\%) & (\%) & (\%) & (\%) \end{array}$
{Urinary system}	[u				
kidney	atypical tubule hyperplasia	<pre> <60> < 0) (0) (0)</pre>	<pre><50> </pre> <pre><50> </pre> <pre>(0)(0)(0)</pre>	<pre> <50> <50> (0) (0) (0)</pre>	(2) (0) (0) (0) (0) (0) (0) (0) (0) (0) (0
urin bladd	dilatation	<pre></pre>	<pre> <50> <50> (0) (0) (0)</pre> (0) (0) (0)	<pre><code <<="" <code="" td=""><td>$\begin{array}{cccc} < 50 \\ & & \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$</td></code></pre>	$\begin{array}{cccc} < 50 \\ & & \\ 1 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$
(Endocrine system)	iem)				
pituitary	angiectasis	$\begin{array}{cccc} <50> & <50> & \\ 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre><50> 7 0 0 0 (_14) (0) (0) (0)</pre>	<pre><50> 2 1 0 0 (4) (2) (0) (0)</pre>	<pre><50> 0 0 1 0 (0) (0) (2) (0)</pre>
	hemorrhage			$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
	cyst	$\begin{bmatrix} 14 & 0 & 0 & 0 \\ (28) & (& 0) & (& 0) \\ \end{array}$	15 0 0 0 0 0 (30) (0) (0)	10 0 0 0 0 (20) (0) (0)	13 1 0 0 (26)(2)(0)(0)
	hyperplasia	7 2 4 0 (14) (4) (8) (0)	8 2 4 0 (16) (4) (8) (0)	5 4 5 0 (10) (8) (10) (0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Test of Chi Square

4 : Severe

BAIS4

(HPT150)

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STUDY NO. ANIMAL REPORT TYPE SEX	: 0675 : RAT F344/DuCrlcrlj[F344/DuCrj] E : Al : FEMALE	HISTOPATHOLOCICAL FINDINGS : ALL ANIMÁLS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	¢	PAGE : 24
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 ppm 50 (%) (%) (%) (%)
{Endocrine system}	system)				
pítuitary	Rathke pouch	$\begin{array}{cccc} \langle 50 \rangle & & \\ 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre><50> 2 0 0 0 (4) (0) (0) (0)</pre>	<pre> <50> <50> (0) (0) (0)</pre>	<pre><50> </pre> <pre><50> </pre> <pre>(4)(0)(0)(0)</pre>
thyroid	inflammatory infiltration	$\begin{array}{ccccc} < 50 \\ & & \\ 0 & 0 & 0 \\ (& 0) & (& 0) & (& 0) \\ \end{array}$	<pre><50> </pre> <pre><50> </pre> 0 0 0 0 (0) (0) (0)	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>	<pre><50> </pre> <pre><50> </pre> <pre>(50)</pre> <pre>(50)</pre> <pre>(60)</pre> <pre>(60)</pre>
	ultimobranchial body remanet		0 0 0 0 0 0 0 (0)	1 0 0 0 0 0 (2) (0) (0)	1 0 0 0 (2)(0)(0)(0)
	follicular hyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	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
	C-cell hyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 2 0 0 (6)(4)(0)(0)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7 0 0 0 (14) (0) (0) (0)
adrenal	peliosis-like lesion	$\begin{pmatrix} 50 \\ 2 \\ 4 \end{pmatrix} (0) (0) (0)$	<pre><50> 3 0 0 0 (6) (0) (0)</pre>	<pre> <50> <50> (50) (4) (10) (10) (10) (10) (10) (10) (10) (10</pre>	<pre><50> </pre> (0) (0) (0)
	increased extramedullary hematopoiesis	ssis 1 0 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)
Grade < a > b (c) Significant	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 Significant difference ; * : P $\leq 0, 05$ ** : P	3 : Marked 4 : Severe > site > ≦ 0.01 Test of Chi Square			

(HPT150)

STUDY NO. : ANIMAL : REPORT TYPE :	: 0675 : RAT F344/DuCrICrIj[F344/DuCrj] : A11 : A11	HISTOPATHOLOGICAL FINDING ALL ANIMALS (0-105%)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)		
	- FEMALE				PAGE : 25
		Control 50 3	100 ppm 50 1 2 3	200 ррш 50 3	400 ppm 50 3
Organ	Findings) (%) (%)	(%) (%) (%)	(%) (%) (%) (%)	<u>1 2 3 4</u> (%) (%) (%)
{Endocrine system}	stem)				
adrenal	hyperplasia:cortical cell	$\begin{array}{cccc} <50> & <50> & \\ 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{array}$	$\begin{array}{cccc} <50 \\ 1 & 1 & 0 \\ (2) & (2) & (0) & (0) \end{array}$	<pre><0></pre> <pre><0></pre> <pre><0</pre> <pre><0</pre> <pre></pre> <pre><</pre>	$\begin{array}{cccc} < 50 \\ 1 & 1 & 0 & 0 \\ (& 2) & (& 2) & (& 0) & (& 0) \end{array}$
	hyperplasia:medulla	$\begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & (& 0) & (& 2) & (& 0) \\ \end{pmatrix}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 1 1 0 (0)(2)(2)(0)	2 0 0 0 (4)(0)(0)(0)
	focal fatty change:cortex	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6 1 0 0 (12)(2)(0)(0)
	necrosis:cortex		0 1 0 0 (0) (2) (0) (0)	(0)(0)(0)(0) 00000000000000000000000000	
{Reproductive system}	system)				
оүагу	cyst	$\begin{array}{cccc} <50> & <50> & \\ 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre><50> 4 0 0 (8) (0) (0) (0)</pre>	$\begin{array}{cccc} <50> & \\ 1 & 0 & 0 & 0 \\ (& 2) & (& 0) & (& 0) \end{array}$	<pre><50> 0 0 0 (0) (0) (0)</pre>
	mesothelial hyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		(0)(0)(0)(0) 0 0 0 0	(0)(0)(0)(0) 0 0 0 0 0
uterus	cystic endometrial hyperplasia	<pre><50> 6 0 0 (12) (0) (0)</pre>	<pre> <50> <50> (0) (0) (0)</pre>	<pre><50></pre> <pre><50></pre> <pre>(10) (0) (0) (0)</pre>	$\begin{array}{cccc} & <50 \\ 7 & 0 & 0 \\ (14) & (0) & (0) & (0) \end{array}$
Grade 1 : Slight < a > a : Number b b : Number b : Number (c) c : b / a * Significant difference ;	1 : Slight 2 : Moderate 3 :] a : Number of animals examined at the site b : Number of animals with lesion c : b / a * 100 ifference : * : P ≤ 0.05 ** : P ≤ 0.	3: Marked 4: Severe We site for a site for a square for the square for the square for the state of the square for the square			

(HPT150)

0675	RAT F344/DuCrlCrlj[F344/DuCri]	Al	FEMALE	
••	••	••	••	
STUDY NO.	ANEMAL	REPORT TYPE : AI	SEX	

Organ Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm 50 (%) (%) (%) (%)	400 jppn 50 (%) (%) (%) (%)
[Reproductive system]				
vagina . cyst	<pre><20></pre> < (0) (0) (0) (0) < (0) (0) (0)	$\begin{array}{cccc} \langle 50 \rangle & & \\ 1 & 0 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre></pre>	<pre><50> </pre> <pre><50> </pre> <pre>(0) (0) (0) (0)</pre>
nammary gl hyperplasia	$\begin{array}{cccc} & <50 \\ & & < \\ 0 & 1 & 0 & 0 \\ (& 0) & (& 2) & (& 0) & (& 0) \end{array}$	<pre><50> <50> </pre> (0) (0) (0) (0)	<pre><code <<="" <code="" td=""><td><pre></pre></td></code></pre>	<pre></pre>
galactocele		2 0 0 0 0 (4) (0) (0)	0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0
(Nervous system)				
brain vacuolic change	$\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 $	$\begin{array}{cccc} <50 \\ 1 & 0 & 0 \\ (2) & (0) & (0) & (0) \end{array}$	<pre><pre><pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre></pre></pre>	<pre></pre>
(Special sense organs/appendage)				
eye cataract	$\begin{array}{ccccc} & \langle 50 \rangle & \\ 1 & 1 & 0 & 0 \\ (& 2) & (& 3) & (& 0) \end{array}$	$\begin{array}{cccc} <50 \\ 1 & 1 & 0 & 0 \\ (& 2) & (& 2) & (& 0) & (& 0) \end{array}$	<pre><50> 1 2 0 0 (2) (4) (0) (0)</pre>	<pre><50> 2 1 0 0 (4) (2) (0) (0)</pre>
Grade 1 : Slight 2 : Moderate 3 :) < a > a : Number of animals examined at the site b b : Number of animals with lesion (c) c : b / a * 100 Significant difference ; * : P ≤ 0.05 *** : P ≤ 0.	3 : Marked 4 : Severe he site P≦0.01 Test of Chi Square			

(HPT150)

STUDY NO.	••	0675
ANIMAL	••	: RAT F344/DuCrlCrlif[F344/DuCri]
REPORT TYPE	••	Al
SEX	٠	FFUAL F

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SEX : FE	: FEMALE				PAGE : 27
Organ	Group Name No. of Anir Grade Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	100 ppm 50 (%) (%) (%) (%)	200 ppm · 50 (%) (%) (%) (%)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
(Special sen	(Special sense organs/appendage)				
еуе	retinal atrophy	<pre><50> (50) (50) (50) (50) (4) (50) (50) (50) (50) (50) (50) (50) (50</pre>	$\begin{array}{cccc} < 50 \\ 0 & 1 & 0 \\ (& 0) & (& 0) \\ \end{array}$	$\begin{array}{cccc} <50> & <50> & \\ 1 & 2 & 1 & 0 & \\ (& 2) & (& 4) & (& 2) & (& 0) \end{array}$	$\begin{array}{ccc} <50> \\ 0 & 1 & 2 & 0 \\ (& 0) & (& 2) & (& 4) & (& 0) \end{array}$
	keratitis	3 1 0 0 (6)(2)(0)(0)	(0)(0)(0)(0) (0)(0)(0)		
	ulcer:cornea	(0) (0) (0) (0) 0 (0) (0) (0)	0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0) 0 0 0 0 0 0)(0)	0 1 0 0 (0) (2) (0) (0)
Harder gl	- degeneration	<pre><30></pre> <pre><30></pre> <pre><30></pre> <pre></pre> <pre><30></pre> <pre></pre>	<pre><50> 1 0 0 (2) (0) (0)</pre>	<pre><50> 1 0 0 (2) (0) (0)</pre>	<pre><50> 2 0 0 4) (0) (0) (0)</pre>
	inflaumation	1 0 0 0 (2)(0)(0)(0)	1 0 0 0 (2)(0)(0)(0)	1 0 0 0 (2)(0)(0)(0)	(0)(0)(0)(0) 0 0 0 0 0
{Musculoskel((Musculoskeletal system)				
muscle	mineralization	<pre><50></pre>	<pre><50> 1 0 0 0 (2) (0) (0) (0)</pre>	<pre> <50> < 0) (0) (0) (0)</pre>	<pre><60></pre> <pre><60></pre> <pre></pre> <pre><60</pre> <pre></pre>
Grade Grade k (c) Significant (Grade 1: Slight 2: Moderate 3: Marked < a > a: Number of animals examined at the site b b: Number of animals with lesion (c) c: b / a * 100 Significant difference ; *: P ≤ 0.05 **: P ≤ 0.01	4 : Severe 1 - Severe			
(HPT150)					

(HPT150)

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N NO. IAL NRT TYPE	HISTOPATHOLOGICAL FINDINGS :1 ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANTMALS (0-105W)	Ю	
SEA : FEMALE				PAGE : 28
	Control 50 2 3	100 ppm 50 2 3	50 3 7	400 ppm 50 1 2 3 4
	(%) (%) (%) (%)	(%) (%) (%)	(%) (%) (%)	(%) (%) (%)
(Musculoskeletal system)				
bone osteosclerosis	50> 0	<02>	<pre>4 1 1 0</pre>	
		(6) (2) (2) (0)		
(Body cavities)				
peritoneum inflammatory infiltration	<50> 0 0	<pre><50> 1 0 0</pre>	<50> 0 0	
	(0)(0)(0)) (0)		<u> </u>
peritonitis				
	3 : Marked 4 : Severe he site			
b b: Number of animals with lesion (c) c: $b / a \approx 100$				
: P ≦ 0.05	** : P ≤ 0.01 Test of Chi Square			
(HPT150)			ana a sa ana ana ana ana ana ana ana ana	BAIS4

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TABLE O1

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NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS : MALE

ANTMAL : RAT F344/DuCr10 SEX : MALE	RAT F344/DuCrlCrlj[F344/DuCrj] MALE	NEOFLADIIC LEDIONS-INCLUENCE AND SIAIISIICAL ANALISIS	SICILARY JE	PAGE : 1
Group Name	Control	100 ppm	200 ppm	400 ррш
Thracks to the second se	SITE : skin/appendage TUMOR : keratoacanthoma			
overall rates(a) Adjusted rates(b)	4/50(8.0) 9.76	2/50(4. 0) 5. 00	2/50(4.0) 4.26	1/50(2.0) 2.38
Terminal rates(c) Statistical analysis Peto test	4/41(9.8)	2/40(5.0)	1/40(2.5)	1/42(2.4)
Standard method(d) Prevalence method(d) Combined analysis(d)	P = P = 0.9034 P =			
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0. 1848	P = 0.3389	P = 0.3389	P = 0.1811
E	SITE : subcutis TUMOR : fibroma			
lumor rate Overall rates(a)	8/50(16.0)	6/50(12.0)	3/50(6.0)	5/20(10.0)
Adjusted rates(b) Terminal rates(c)	17.07 7/41 (17.1)	11.63 4/40(10.0)	6.67 2/40(5.0)	10.87 4/42(9.5)
Peto test Peto test Standard method(d) Prevalence method(d) Combined analysis(d)	P = 0. 8798 P = 0. 7255 P = 0. 8299			
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.3206	P = 0.3871	P = 0. 0999	P = 0.2768
e	SITE : lung TUMOR : bronchiolar-alveolar adenoma			
lumor rate Overall rates(a) Adinsted rates(h)	3/50(6.0) 7.32	4/50(8.0)	3/50(6.0) 7 E0	0/20(0,0)
Terminal rates (c) Statistical analysis	3/41(7.3)	4/40(10.0)	3/40(7.5)	0,42(0.0)
Feto test Standard method(d) Prevalence method(d) Combined analysis(d)	P = P = 0.9567			
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.0999	P = 0.5000	P = 0.6611	P = 0.1212

(HPT360A)

STUDY No. : 0675 ANIMAL : RAT F344/DuCrIC SEX : MALE	0675 RAT F344/DuCrlCrlj[F344/DuCrj] MALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	al analysis	PAGE : 2
Group Name	Control	100 ppm	200 ррт	400 ppm
,	SITE : lung TUMOR : bronchiolar-alveol	lung bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma		-
lumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c)	5/50(10.0) 12.20 5/41(12.2)	4/50(8.0) 10.00 4/40(10.0)	3/50(6.0) 7.50 3/40/75	0/50(0.0) 0.0 0.492(0.0)
Statistical analysis Peto test method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.0268*	P = 0.5000	$V_{0} = 0.3575$	
	SITE : spleen TUMOR : mononuclear cell leukemia	eukemia		
Tumor rate Overall rates(a)	50(3/50/ 6 0)	9/ED(A D)	1 /50/ 2 0)
Adjusted rates(b)	2.44		2.50	2.38
Terminal rates(c) Statistical analysis	1/41(2.4)	1/40(2.5)	1/40(2.5)	1/42(2.4)
Peto test Standard method(d) Prevalence method(d) Combined analysis(d)	P = 0.9694 P = 0.4932 P = 0.9198			
Countain Armitage test(e) Fisher Exact test(e)	r = 0.1539	· P = 0.5000	P = 0.3389	P = 0. 1811
ſ	SITE : liver TUMOR : hepatocellular adenoma	inoma		
Overall rates (a)	0/50(0.0)	4/50(8.0)	0/50(0.0)	1/50(2.0)
Terminal rates(c) Statistical analysis	0/41(0.0)	4/40(10.0)	0/40(0.0)	0/42(0.0)
Peto test Standard method(d) Prevalence method(d) Combined analysis(d)	P = P = 0.5767 P =			
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.8183	P = 0.0587	P = N.C.	P = 0.5000

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(HPT360A)

STUDY No. : 0675 ANIMAL : RAT F344/DuCr1 SEX : MALE	0675 RAT F344/buCrlCrlj[F344/buCrj] MALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	ISTICAL ANALYSIS	с цута
				- 200 -
Group Name	Control	loo ppm	200 ppm	400 ppm
	SITE : pancreas TUMOR : islet cell adenoma			
Tumor rate				
Overall rates(a)	3/50(6.0)	2/50(4.0)	7/50(14.0)	2/50(4.0)
	7.32	5.00	16.28	4.76
Terminal rates(c) Statistical analysis	3/41 (7.3)	2/40(5.0)	6/40(15.0)	2/42 (4.8)
Peto test				
Standard method(d)	P =			
Prevalence method(d)	P = 0.5300			
Combined analysis(d)				
Cochran-Armitage test(e)	P = 0.9254			
Fisher Exact test(e)		P = 0.5000	P = 0.1589	P = 0.5000
	SITE : pancreas TUMOR : islet cell adenoma	pancreas islet cell adenoma islet cell adenocarcinoma		
Tumor rate				
Overall rates(a)	4/50(8.0)	2/50(4.0)	7/50(140)	9/EU(4 U)
Adjusted rates(b)	9.76		16.28	
Terminal rates(c)	4/41(9.8)	2/40 (5.0)	6/40(15.0)	2/42 (4.8)
Statistical analysis				
Peto test				
Standard method(d)	p =			
Prevalence method(d)	P = 0.6522			
Combined analysis(d)	P =			
Cochran-Armitage test(e)	P = 0.6830			
Fisher Exact test(e)		P = 0.3389	P = 0.2623	P = 0.3389
	••			
	TUMOR : adenoma			
Tumor rate				
Overall rates(a)	13/50(26.0)	5/50(10.0)	16/50(32.0)	6/50(12.0)
Adjusted rates(b)	29.27	10.00	35.00	11.11
Terminal rates(c)	12/41(29.3)	4/40(10.0)	14/40 (35.0)	4/42(9.5)
Statistical analysis				
Peto test				
Standard method(d)				
	P = 0.8900			
Contract analysis (d)	F = 0.8034			
COCALFARTALTAGE LEST (e)	Y = 0.2821			
LISHEL DYACT LESI (6)		$\Gamma = 0, 0.332*$	P = 0.3299	Y = 0.0524

(HPT360A)

STUDY No. : 0675 ANTMAL : RAT F344/DuCr SEX : MALE	0675 RAT F344/bucrlcrlj[F344/bucrj] MALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	ISTICAL ANALYSIS	PA	PAGE : 4
Group Name	Control	порадиния 100	200 ppm	400 ppm	
e	SITE : pituitary gland TUMOR : adenoma,adenocarcinoma				
	13/50(26.0) 29.27	5/50(10.0) 10.00	16/50(32.0) 35.00	6/50(12.0) 11.11	
Terminal rates(c) Statistical analysis	12/41(29.3)	4/40(10.0)	14/40(35.0)	4/42(9.5)	
	P = 0. 4521 P = 0. 8900 P = 0. 8634 P = 0. 2821				
Fisher Exact test(e)		P = 0,0332*	P = 0.3299	P = 0.0624	
Timor vata	SITE : thyroid TUMOR : C-cell adenoma				
Overall rates(a) Addinsted rates(b)	3/50(6.0) 7 32	8/50(16.0) 17 50	9/50(18.0)	3/50(6.0)	
Terminal rates(c) Statistical analysis	3/41(7.3)	7/40(17.5)	8/40(20.0)	3/42(7,1)	
Peto test Standard method(d) Prevalence method(d) Combined analysis(d)	P = 0. 3948 $P = 0. 6421$ $P = 0. 6233$				
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.7360	P = 0. 0999	P = 0.0606	P = 0.6611	
T	SITE : thyroid TUMOR : C-cell carcinoma	-			
lumor fave Overall rates(a) Adinsted rates(h)	3/50(6.0) 4.76	1/50(2.0)	1/50(2.0)	1/50(2.0)	
Terminal rates(c) Statistical analysis Doto + + + +	1/41(2.4)	0/40(0.0)	1/40(2.5)	0/42(0.0)	
reconvest Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e)	P = 0.5139 P = 0.8995 P = 0.8273 P = 0.3266				
Fisher Exact test(e)		P = 0.3087	P = 0.3087	P = 0.3087	

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(HPT360A)

STUDY No. : 0675 ANTMAL : RAT F344/DuCr10 SEX : MALE	0675 RAT F344/DuCrlCrlj[F344/DuCrj] MALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	STICAL ANALYSIS	. PAGE : 5
Group Name	Control	100 ppm	200 ррп	400 ppm
Timor vəfa	SITE : thyroid TUMOR : C-cell adenoma,C-cell carcinoma	ell carcinoma		
Overall rates (a) Overall rates (a) Adjusted rates (b) Terminal rates (c) Statistical analysis	6/50(12.0) 11.90 4/41(9.8)	9/50(18.0) 17.50 7/40(17.5)	10/50(20.0) 22.50 9/40(22.5)	4/50(8.0) 7.14 3/42(7.1)
Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.4785 P = 0.7874 P = 0.7662 P = 0.4349	P = 0.2883	P = 0.2070	P = 0.3703
Ē	SITE : adrenal gland TUMOR : pheochromocytoma			
lumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statitical analucia	2/50(4.0) 4.88 2/41(4.9)	4/50(8.0) 10.00 4/40(10.0)	2/50(4. 0) 5. 00 2/40(5. 0)	4/50(8.0) 9.52 4/42(9.5)
Peto test Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0.2859 P = 0.5459 P = 0.5459	P = 0.3389	P = 0.6913	P = 0.3389
Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis	SITE : adrenal gland TUMOR : pheochromocytoma,p 4/50(8.0) 7.32 3/41(7.3)	adrenal gland pheochromocytoma, pheochromocytoma:malignant 8.0) 5/50(10.0) 7.32 12.50 7.3) 5/40(12.5)	2/50(4. 0) 5. 00 2/40(5. 0)	4/50(8.0) 9.52 4/42(9.5)
Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.9139 ? P = 0.4740 P = 0.5966 P = 0.8205	P = 0.5000	P = 0.3389	P = 0.6425

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(HPT360A)

STUDY No. : 0675 ANIMAL : RAT F344/DuCr10 SEX : MALE	0675 RAT F344/buCrlcrlj[F344/buCrj] MALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	STICAL ANALYSIS		PAGE : 6
Group Name	Control	100 ррт	200 ppm	400 ppm	
Timos soto	SITE : testis TUMOR : interstitial cell tumor	or			
overall rates (a) Overall rates (a) Adjusted rates (b) Terminal rates (c) Statistical analysis	44/50(88.0) 95.56 39/41(95.1)	46/50(92.0) 97.62 39/40(97.5)	40/50(80.0) 88.37 35/40(87.5)	42/50(84.0) 93.02 39/42(92.9)	
Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0.8073 P = P = 0.3348	P = 0. 3703	P = 0.2070	P = 0.3871	
Ę	SITE : mammary gland TUMOR : fibroadenoma				
	0/50(0.0) 0.0 0/41(0.0)	3/50(6.0) 6.52 1/40(2.5)	0/50(0.0) 0.0 0/40(0.0)	1/50(2.0) 2.38 1/42(2.4)	
Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0.4770 P = P = 1.0000	P = 0. 1212	P = N.C.		
Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	SITE : mammary gland TUMOR : adenoma, fibroadenoma, adenocarcinoma 0/50(0.0) 3 0/41(0.0) 1 0/41(0.0) 1 P = 0.4770 P = 0.4770 P = 1.0000 P = 1.0000 P = 1.0000	adenocarcinoma 3/50(6.0) 6.52 1/40(2.5) P = 0.1212	0/50(0.0) 0.0 0/40(0.0) P = N.C.	1/50(2.0) 2.38 1/42(2.4) P = 0.5000	

STUDY No. : 0675 ANIMAL : RAT F344/DuCrlCrlj[F344/DuCrj] SEX : MALE	1 j [F344/DuCr j]	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	stical analysis	PAGE :	2
Group Name	Control	ndq 100	200 ppm	400 ppm	
	SITE : peritoneum TUMOR : mesothelionna				
Tumor rate					
Overall rates(a)	3/50(6.0)	2/50(4.0)	0/20(0)	3/50/ 6 0)	
Adjusted rates(b)	7.32				
Terminal rates(c)	3/41 (7.3)	2/40(5.0)	0/40(0.0)	3/42(7.1)	
puduisuical analysis Peto test					
Standard method(d)	D ≡				
Prevalence method (d)	P = 0 = 0.000				
Combined analysis(d)	P =				
Cochran-Armitage test(e)	P = 1,0000				
Fisher Exact test(e)		P = 0.5000	P = 0.1212	P = 0.6611	
(IDT9604)					
(HP136UA)				BAI	BAIS4
 (a): Number of tumor-bearing animals/number of (b): Kaplan-Meier estimated tumor incidence at (c): Observed tumor incidence at terminal kill. (d): Beneath the control incidence are the P-va Standard method : Death analysis Frevalence method : Death analysis Prevalence method : Incidental tumor test Combined analysis : Beath analysis + Inc (e): The conditional probabilities of the large ? Ther onditional probabilities of the large : There is no data which should be stat Significant difference ; * : P ≤ 0.05 M.C.:Statistical value cannot be caloniated and 	 (a): Number of tumor-bearing animals/number of animals examined at the (b): Kaplan-Meier estimated tumor incidence at the end of the study aft (c): Observed tumor incidence at terminal kill. (d): Beneath the control incidence are the P-values associated with the Standard method : Death analysis (d): Beneath the control incidence are the P-values associated with the Standard method : Death analysis (e): The Cochran-Armitage and Fisher exact test compare directly the ov Combined analysis is the largest and smallest possible fee for the Cochran-Armitage and Fisher exact test compare directly the over the conditional probabilities of the largest and smallest possible for the fiftherence is a statistical analysis. Significant difference is at the conducted and wee not conditional value to the calculated and wee not conditional value. 	ned at the s e study afte ed with the dest test test test sis.	ite. r adjusting for intercurrent mortality. trend test. rall incidence rates. out comes can not estimated or this P-value is beyond the estimated P-value.		
		1911TT TCOULS			

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TABLE O2

NEOPLASTIC LESIONS-INCIDENCE

AND STATISTICAL ANALYSIS : FEMALE

Group Name	Control	100 ppm	200 ppm	400 ppm	
	SITE : spleen TUMOR : mononuclear cell leukemia				
Tumor rate					
Overall rates(a)	2/50(4.0)	7/50(14.0)	0/50(0.0)	1/50(2.0)	
Adjusted rates(b) Terminal rates(c)	2. 63 1/38(2, 6)	13.89 5/36/13-0)	0.0	0.0	
Statistical analysis					
reto test Standard method(d)	P = 0 6189				
Prevalence method(d)					
Combined analysis(d)	P = 0.9247				
Cochran-Armitage test(e) Fisher Event test(e)	P = 0.1539				
risner EXact test(e)	,	P = 0.0798	P = 0.2475	P = 0.5000	
	SITE : pituitary gland				
Tumor rate					
Overall rates(a)	21/50(42.0)	18/50(36.0)	10/50/ 38 0)	15/50(30 D)	
Adjusted rates(b)	43. 59	38, 89	19/00/00.0/ 34.88	10/00/00/00	
Terminal rates(c)	16/38(42.1)	14/36 (38.9)	15/43(34.9)	10/36(27.8)	
Statistical analysis Pato tost					
standard mothod(d)	D - 0 5011				
Drouglong mothod (J)	$\Gamma = 0.0041$ D = 0.0063				
Combined analysis(d)	F = 0.0903 P = 0.8551				
Cochran-Årmitage test(e)	P = 0.2433				
Fisher Exact test(e)		P = 0.3410	P = 0.4192	P = 0.1488	
	STTF : nituitary aland				
Tumor rate					
Overall rates(a)	21/50(42.0)	18/50(36.0)	19/50(38.0)	17/50(34.0)	
Adjusted rates(b)	43.59	38.89	34.88	29.73	
lerminal rates(c) Statistical analysis	16/38(42.1)	14/36(38.9)	15/43(34.9)	10/36(27.8)	
<pre>Peto test</pre>					
brevalence method(d) Prevalence method(d)	P = 0.2430 P = 0.8953				
Combined analysis(d)	P = 0.7322				
Cochran-Armitage test(e)	P = 0.4740				
LISHEL EXACT LEST(E)		P = 0.3410	Y = 0.419Z	Y = 0.2084	

SEX : FEMALE				PAGE :
Group Name	Control	100 ppm	200 ppm	400 ppm
-	SITE : thyroid TUMOR : C-cell adenoma			
lumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis	7/50(14.0) 18.42 7/38(18.4)	6/50(12.0) 13.95 5/36(13.9)	4/50(8.0) 9.30 4/43(9.3)	0/50(0.0) 0.0 0/36(0.0)
Feto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0.9982 P = P = 0.0069**	P = 0.5000	P = 0.2623	P = 0.0062 ** *
	SITE : thyroid TUMOR : C-cell adenoma, C-cell carcinoma	-cell carcinoma		
Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c)	9/50(18.0) 23.68 9/38(23.7)	7/50(14.0) 16.67 6/36(16.7)	4/50(8.0) 9.30 4/43(9.3)	1/50(2.0) 2.78 1/36(2.8)
Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0. 9985 P = P = 0. 0056**	P = 0. 3929		
	SITE : adrenal gland TUMOR : pheochromocytoma			
Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis	00(88(1/50(2.0) 2.78 1/36(2.8)	3/50(6.0) 6.98 3/43(7.0)	2/50(4.0) 5.56 2/36(5.6)
reto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = P = 0. 1018 P = 0. 2072	P = 0.5000	P = 0. 1212	P = 0.2475

(HPT360A)

roup Name SIT SIT TUM tes(a) ates(b) ates(c)					
SIT TUM tes(a) ates(b) ates(c)	Control	100 ppm	200 ppm	400 ppm	
tes(a) ates(b) ates(c)	3 : adrenal gland 3R : pheochromocytoma.melienat	comocytoma;ma]ionant			
tes(a) ates(b) ates(c)		· · · · · · · · · · · · · · · · · · ·			
ates (b) ates (c)	1/50(2.0)	1/50(2.0)	3/50(6.0)	3/50(6.0)	
ates(c)					
Statistical analysis	1/38(2.6)	1/36(2.8)	3/43(7.0)	3/36(8.3)	
d					
<u>م</u> ہ	= 0.1068				
Cochran-Armitage test(a) D:	= 0 2225				
-	0. 111	P = 0.7525	P = 0.3087	P = 0.3087	
SITE	·				
Tumor rate	AN · endometrial stromal polyp	4			
ites(a)	13/50(26.0)	3/50(60)	19/50(34 0)	7 (60/ 14 0)	
	28.95	8.33	17/00/27/01	(0.141)06/1 16.67	
	11/38(28.9)	3/36(8,3)	12/43 (27 9)	10.01 6/36/ 16 7)	
Statistical analysis					
C+understand (L)					
-	F = 0.9104 ?				
	P = 0.7048				
	= 0.7751				
-Armitage test(e)	= 0.4316				
risher Exact test(e)		P = 0.0061**	P = 0.5000	P = 0.1054	
SITE	••				
TUMOR)R : fibroadenoma				
+(-)					
_	0/ 00/ 10. 0)	4/50(8.0)	3/50(6.0)	5/50(10.0)	
	[30, 10 D]	4.26	6.98		
	J/ 301 13. 7J	1/30(2.8)	3/43 (7.0)	1/36(2.8)	
method (d) P	= 0.1652				
e method(d)	= 0.7003				
	P = 0.4832				
ge test(e)	= 0.9658				
risner Exact test(e)		P = 0.5000	P = 0.3575	P = 0.6297	

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STUDY No. : 0675 ANIMAL : RAT F344/DuCr SEX : FEMALE	0675 RAT F344/buCrlCrlj[F344/buCrj] FEMALE	NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	STICAL ANALYSIS		PAGE : 11
Group Name	Control	nada 100	200 ppm	400 ppm	
Tumor rate	SITE : mammary gland TUMOR : adenoma,fibroade	mammary gland adenoma, fibroadenoma, adenocarcinoma			
Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis	6/50(12.0) 13.16 5/38(13.2)	4/50(8.0) 2.78 1/36(2.8)	5/50(10.0) 11.63 5/43(11.6)	7/50(14.0) 11.90 3/36(8.3)	
Feto test Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)	P = 0. 4431 P = 0. 3175 P = 0. 3213 P = 0. 5928	P = 0.3703	P = 0.5000	P = 0.5000	
<pre>(HPT360A) (a): Number of tumor-bearing animals/number of (b): Kaplan-Meier estimated tumor incidence at (c): Observed tumor incidence at terminal kill. (d): Beneath the control incidence are the P-va Standard method : Death analysis revalence method : Incidental tumor test Combined analysis: Death analysis + Inc (e): The Cohran-Arunitage and Fisher aract test ? The conditional probabilities of the large ?: There is no data which should be stat Significant difference ; *: P ≤ 0.05 * N.C.:Statistical value cannot be calculated and</pre>	PT350A) (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 ad (c): Observed tumor incidence at terminal kill. (d): Beneath the control incidence are the P-values associated with the tren Standard method : Death analysis Prevalence method : Incidental tumor test Combined analysis + Incidental tumor test Combined analysis : Death analysis + Incidental tumor test (e): The Cochran-Ammitge and Fisher exact test compare directly the overall ? The conditional probabilities of the largest and smallest possible out 	aftes the s	ite. r adjusting for intercurrent mortality. trend test. rall incidence rates. out comes can not estimated or this P-value is beyond the estimated P-value.	ted P-value.	BAIS4

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TABLE Q1

CAUSE OF DEATH : MALE

PAGE : 1 BAIS4 COUSE OF DEATH (SUMMARY) (0-105W) 400 ppm 8 0 000000 0 0 0 2 0 200 ppm 10 3 0 0 0 0 11 10 -00000 -100 ppm 10 0 0 0 -00 00 -----: 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : MALE Control 6 0 0 0 m o - o o --0 ~ - 0 0 no microscop confirm pneumonia tumor d:spinal cord tumor d:Zymbal gl tumor d:bone urinary retention tumor d:leukemia tumor d:skin/app tumor d:subcutis Number of Dead and tumor d:liver tumor d:kidney tumor d:pituitary tumor d:thyroid tumor d:adrenal tumor d:retroperit Moribund Animal tumor d:brain Group Name STUDY NO. ANIMAL (BI0120) SEX

TABLE Q2

CAUSE OF DEATH : FEMALE

PAGE : 2 BAIS4 COUSE OF DEATH (SUMMARY) (0-105W) 400 ppm 14 0 0 0 - 0 0 0 0 0 0 -0 200 ppm 2 000 4 1 0 0 0 1 0 0 0 0 100 ppm 14 0 0 0 1 1 3 0 4 0 0 0 7 1 2 : 0675 : RAT F344/DuCrlCrlj[F344/DuCrj] : FEMALE Control 12 0 0 0 0 чо 4210 0 0 no microscop confirm peritonitis tumor d:leukemia tumor d:lymph node tumor d:stomach tumor d:small intes tumor d:pəriph nerv tumor d:Zymbal gl tumor d:muscle tumor d:mammary gl tumor d:prep/cli gl tumor d:brain Number of Dead and Moribund Animal tumor d:pituitary tumor d:uterus Group Name STUDY NO. ANTMAL SEX (BI0120)

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FIGURES

FIGURE 1	2,4-PENTANEDIONE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM
FIGURE 2	SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR
	INHALATION STUDY OF 2,4-PENTANEDIONE
FIGURE 3	SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR
	INHALATION STUDY OF 2,4-PENTANEDIONE
FIGURE 4	BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR
	INHALATION STUDY OF 2,4-PENTANEDIONE
FIGURE 5	BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR
	INHALATION STUDY OF 2,4-PENTANEDIONE
FIGURE 6	FOOD CONSUMPTION CHANGES OF MALE RATS IN THE
	2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE
FIGURE 7	FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE
	2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

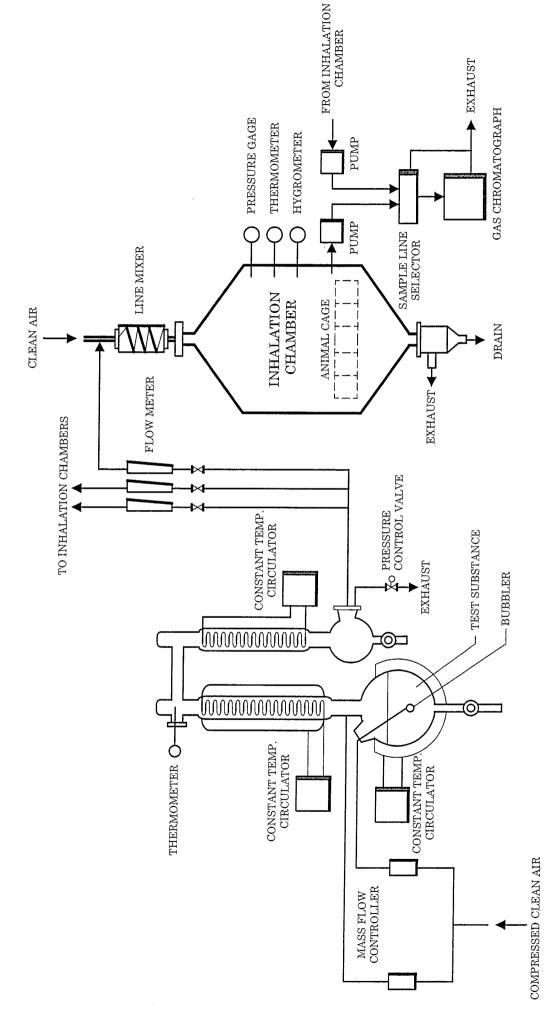


FIGURE 1 2,4-PENTANEDIONE VAPOR GENERATION SYSTEM AND INHALATION SYSTEM

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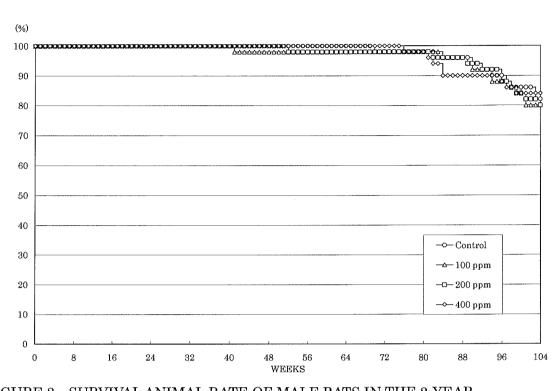


FIGURE 2 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

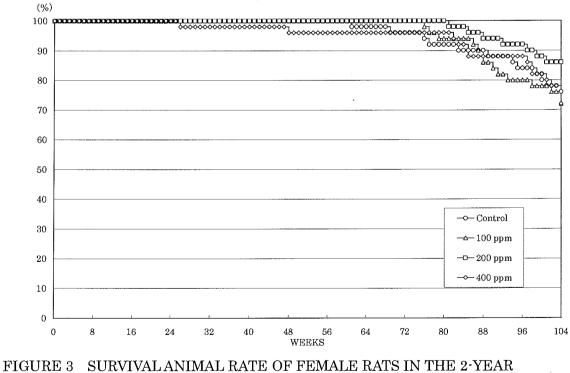


FIGURE 3 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

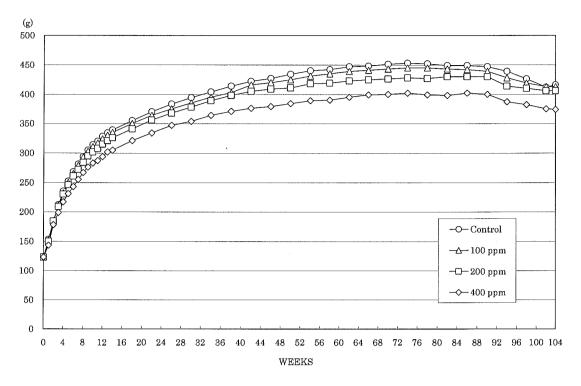


FIGURE 4 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

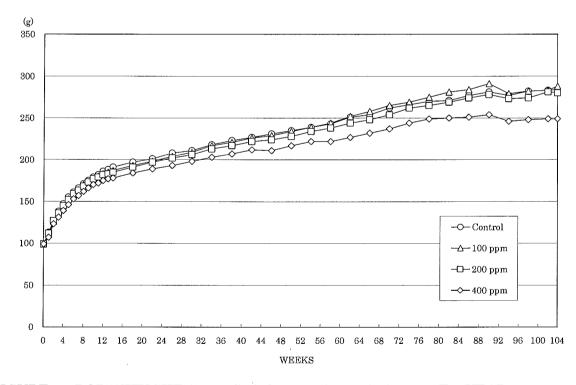


FIGURE 5 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

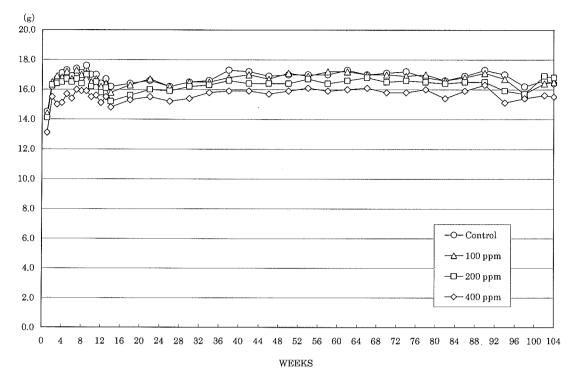


FIGURE 6 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

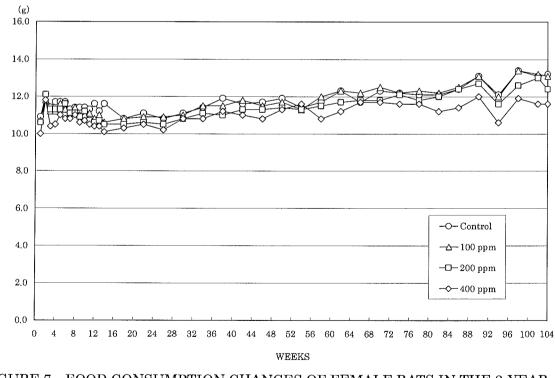
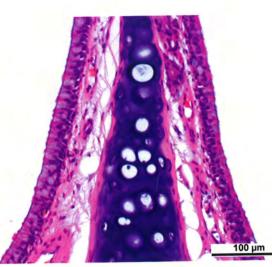


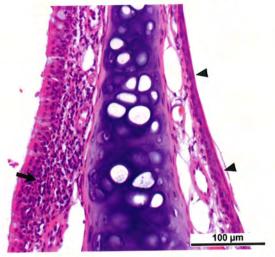
FIGURE 7 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF 2,4-PENTANEDIONE

(Study No. 0675)



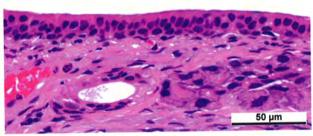
Photograph 1

Nasal cavity (Level 1): Normal (respiratory epithelium) Rat, Female, Control, Animal No. 0675-2035 (H&E)

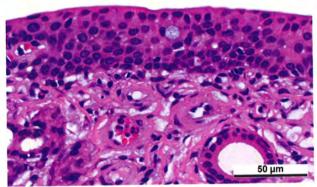


Phograph 2

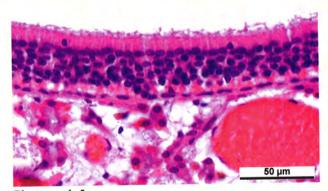
Nasal cavity (Level 1): Squamous metaplasia (arrowheads) of the respiratory epithelium and inflammation (arrow) Rat, Female, 400 ppm, Animal No. 0675-2303 (H&E)



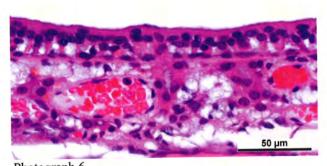
Photograph 3 Nasal cavity (Level 1): Normal (transitional epithelium) Rat, Male, Control, Animal No. 0675-1003 (H&E)



Photograph 4 Nasal cavity (Level 1): Hyperplasia of the transitional epithelium Rat, Male, 400 ppm, Animal No. 0675-1320 (H&E)



Photograph 5 Nasal cavity (Level 2): Normal (olfactory epithelium) Rat, Female, Control, Animal No. 0675-2030 (H&E)



Photograph 6 Nasal cavity (Level 2): Atrophy of the olfactory epithelium Rat, Female, 400 ppm, Animal No. 0675-2307 (H&E)