# Summary of Feed Carcinogenicity Study of Diphenylamine in B6D2F1 Mice

August 2011

Japan Bioassay Research Center

Japan Industrial Safety and Health Association

#### **PREFACE**

The tests were contracted and supported by the Ministry of Health, Labour and Welfare of Japan. The tests were conducted by Japan Bioassay Research Center (JBRC) and the report was prepared by JBRC and peer reviewed by outside expert pathologist. Complete report was submitted to Ministry of Health, Labour and Welfare of Japan on August 25, 2011.

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

## Summary of Feed Carcinogenicity Study of Diphenylamine in B6D2F1 Mice

#### Purpose, materials and methods

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

The carcinogenicity and chronic toxicity of diphenylamine were examined in B6D2F1/Crlj mice. Groups of test animals were administered diphenylamine in their food for 2 years (104 weeks). Each group consisted of either 50 male or 50 female mice. The dietary concentration of diphenylamine were 0, 250, 1000 or 4000 ppm (w/w). Both sexes were administered each concentration of diphenylamine. The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in a previous 13-week toxicity study. The identity of the diphenylamine used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by high performance liquid chromatography before and after use to affirm its stability. The concentrations of diphenylamine in the diet were determined by high performance liquid chromatography at the time of preparation and on the 8th day after preparation while stored at room temperature or stored in the refrigerator. The animals were observed daily for clinical signs and mortality. Body weight, water consumption and food consumption were measured once a week for the first 14 weeks and every 4 weeks thereafter. Animals found dead, in a moribund state, or surviving to the end of the 2-year administration period underwent complete necropsy. Urinalysis was performed near the end of the administration period. Hematology and blood biochemistry analysis were performed at the terminal necropsy: surviving animals were fasted overnight and bled under deep ether anesthesia. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were then fixed and embedded in paraffin. Five µm thick tissue sections were prepared and stained with hematoxylin and eosin and examined microscopically. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. Any positive dose-response trends of diphenylamine induction of neoplastic lesions were analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by the Chi-square test. Changes in body weight, water consumption, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory

Practice and with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

#### **Results**

The markedly decreased survival rate of the 4000 ppm-fed male group was attributed to the increased number of deaths due to urinary retention. Survival rates of the females fed 4000 ppm inceased more than the female control at the end of administration period. Brown urine was observed in the 4000 ppm-fed males and females. Body weights were supressed in males fed 4000 ppm diphenylamine throughout the 2-year administration period and in females fed 4000 ppm diphenylamine after 18th week of the administration period. Food consumption in the all administerd group were similar to the respective controls. Due to the markedly decreased survival rate caused by urinary retention and the marked body weights supression, the high dose level of 4000 ppm for males was considered to exceed the MTD.

The incidences of selected neoplastic lesions in male and female mice are presented in the tables below. The combined incidence of hemangioma and/or hemangiosarcoma in spleen was increased in males fed 1000 ppm (Fisher's exact test). The incidence of hemangioma in all organs including subcutis, bone marrow, spleen, liver and heart was increased in males (Peto test), and the incidence of hemangioma and the combined incidence of hemangioma and/or hemangiosarcoma was increased in males fed 1000 ppm (Fisher's exact test). The incidence of histiocytic sarcoma in uterus was increased in female mice fed 1000 ppm diphenylamine. But the incidence was within the range of maximum incidence of the JBRC historical control data, so the incidence of histiocytic sarcoma in uterus can not be judged to be attributed to the diphenylamine administration. No significant diphenylamine related increase in incidence of neoplastic lesions was found in females.

In blood and hematopoietic system, methemoglobin concentration was increased in all groups of males and females fed diphenylamine. Anemia caused by the increase of methemoglobin concentration was observed in all groups of males and females fed diphenylamine. Also vearious anemia-related changes in hematology and biochemistry were observed in diphenylamine-fed groups. In the bone marrow, increased hematopoiesis was observed. In the spleen, increased organ weights, increased extramedullary hematopoiesis, deposit of hemosiderin and engorgement of erythrocyte were observed. Deposit of hemosiderin was observed also in liver and kidney. In the liver, hepatocellular hypertrophy were increased in males and females fed 4000 ppm. In the urinary system, urinary retention was observed in males fed 4000 ppm. Plasma urea nitrogen was increaded in females fed 4000 ppm. Kidney weights

were increased in femels fed 1000 ppm above, pyelonephritis was observed in males fed 4000 ppm. In the urinary bladder, dilatation was observed in males fed 4000 ppm and hyaline droplet degeneration was observed in both males and females fed 4000 ppm. The inflammation in urethra was observed in males fed 4000 ppm. In lung, uremic pneumonitis was increased in males fed 4000 ppm and degeneration of blood vessel was observed in both males and females fed 4000 ppm.

In the present two-year feeding study, the effects on blood and hematopoietic system were observed for the lowest dose of 250 ppm in both males and females. The lowest observed-adverse-effect-level (LOAEL) of diphenylamine in the diet was 250 ppm (male : 29 mg/kg body weight per day).

#### **Conclusions**

There was some evidence for carcinogenicity of diphenylamine in male mice based on the increased incidences of vascular tumours in spleen and in all organs included spleen and liver. There was no evidence for carcinogenicity of diphenylamine in female mice.

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

	Dose (ppm)	0	250	1000	4000	Peto test	Cochran- Armitage test
Number of exa	mined animals	50	50	50	50		
benign tumor							
subcutis	hemangioma	0	0	1	0		
lung	bronchiolar-alveolar adenoma	5	4	7	4		
bone marrow	hemangioma	0	0	0	1		
spleen	hemangioma	1	0	6	2		
liver	hemangioma	2	2	5	3	<b>1</b>	
	hepatocellular adenoma	9	14	10	2 *		$\downarrow\downarrow$
Harderian gland	adenoma	4 <sup>a)</sup>	2	1	1		
malignant tume	or						
lung	bronchiolar-alveolar carcinoma	5	6	8	1		
lymph node	malignant lymphoma	6	4	3	2		
spleen	hemangiosarcoma	0	0	3	1		
heart	hemangiosarcoma	0	1	0	0		
liver	histiocytic sarcoma	5	1	1	1		
	hepatocellular carcinoma	7	15 *	5	2		$\downarrow \downarrow$
	hemangiosarcoma	0	1	2	1		
epididymis	histiocytic sarcoma	1	1	3	1		
spleen	hemangioma+hemangiosarcoma	1	0	9 **	3		
liver	hemangioma+hemangiosarcoma	2	3	7	4	<b>↑</b>	
all organs b)	hemangioma	3	2	10 *	6	1	
	hemangiosarcoma	0	1	4	1		
	hemangioma + hemangiosarcoma <sup>c)</sup>	3	3	14 **	6		

#### Significant difference

b: All organs were consisted of spleen, liver, subcutis, bone marrow and heart.

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

a: Number of animals examined is 49

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

						Peto	Cochran-
	Dose (ppm)	0	250	1000	4000	test	Armitage
							test
Number of ex	camined animals	50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	1	3	1	2		
liver	hepatocellular adenoma	4	4	3	0		$\downarrow$
pituitary	adenoma	2	0	5	4		
Harderian gland	adenoma	0	3	1	2		
malignant tur	nor						
lymph node	malignant lymphoma	18	20	17	15		
spleen	malignant lymphoma	0	3	1	0		
liver	histiocytic sarcoma	4	0	1	1		
	hemangiosarcoma	1	1	2	3		
uterus	histiocytic sarcoma	8	7	17 *	12		

#### Significant difference

1. p \(\geq 0.03\) (1 islici tes	*: p≦0.05	**: p≦0.01	(Fisher test
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## TABLE C 1

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS: MALE

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MEAN BODY WEIGHTS AND SURVIVAL

PAGE : I

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Cr1j[Crj:BDF1]
UNIT : R
REFORT TYPE : A1 104
SEX : MALE

# of Court. (500) ppm   # of Court. (500) ppm   100 ppm
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#### TABLE C 2

BODY WEIGHT CHANGES AND SURVIVAL ANIMAL NUMBERS: FEMALE

(BI0040)

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Cr1j[Cr.j:BDF1]
UNIT : K
REPORT TYPE : A1 104
SEX : FEMALE

	Control	TO.T	-	undd nez		•	1000 ppm		4	4000 ppm		
Week on Study	Av. Wt.	No.of Surviv. <50>	Av. Wt.	% of cont. (50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	Av. Wt.	% of cont. <50>	No. of Surviv.	
0	19.0 (50)	50/50		100	50/50	- 1	100	50/50	1 -	100	50/50	
1	19.3 (50)	20/20		101	50/50		101	50/50	_	001	50/50	
2		20/20		100	20/20		66	50/20	_	86	50/50	
က	60	50/50	20.4 (50)	100	20/20	20, 2 (50)	100	50/50	20, 1 (50)	66	50/50	
4	_	20/20		100	50/50		101	50/50	_	100	50/20	
ιΩ	21.2 (50)	20/20		100	50/50		101	50/50	_	66	50/50	
9	~	20/20	21.8 (50)	100	50/50		100	20/20	21.5 (50)	66	50/50	
7	_	20/20		101	20/20		100	20/20	21.9 (50)	66	20/20	
œ	~	20/20	22.6 (50)	100	20/20		66	20/20		86	20/20	
6	_	20/20		100	20/20		66	50/50		86	50/50	
10	6	20/20		101	20/20		101	20/20		100	50/50	
11		20/20		66	20/20		66	20/20		86	50/50	
77		50/50		001	20/20		66	50/50		97	50/50	
13		20/20		101	20/20		100	50/50		86	50/50	
14		20/20		100	50/50		100	50/50	23.7 (50)	86	50/50	
18	25.8 (50)	20/20	26.0 (50)	101	20/20		66	50/50		95	50/50	
22		20/20		101	20/20		86	50/50	25.7 (50)	93	50/50	
26		20/20		102	50/50		100	20/20		93	50/50	
30	30.2 (49)	49/50		102	20/20		66	49/50		06	50/50	
34		49/50	32, 7 (50)	103	20/20		86	49/50		87	50/50	
38		49/50		102	20/20		86	49/50		98	50/50	
42	33.8 (49)	49/20	34.2 (50)	101	20/20		98	49/50		98	50/50	
46		49/50		102	50/50		86	19/50		84	50/50	
50	35.3 (49)	49/50	35.6 (49)	101	49/50		96	49/50	29.6 (50)	84	50/50	
54		48/50		100	49/50		96	49/50		83	50/50	
58	36.8 (47)	47/50		100	48/50		96	49/20		84	50/50	
29		47/50		100	48/50		86	48/50		84	49/50	
99	_	47/50		101	48/50		26	47/50		84	49/50	
70	_	47/50		100	46/50		96	47/50		82	48/50	
74	37.9 (47)	47/50	_	66	43/50		96	46/50		83	47/50	
28	_	42/50		86	42/50	_	96	44/50		82	46/50	
85	_	40/20	===	88	41/50	_	97	44/50	31.5 (45)	82	45/50	
98	-	37/20	-	101	40/20	_	86	39/20		83	45/50	
06	-	34/50	_	66	37/50	37.4 (36)	86	36/20		83	42/50	
94	_	32/50	_	100	34/50	_	26	30/20	31.8 (41)	82	41/50	
86	~	30/20	_	103	30/20	_	100	29/20	_	88	41/50	
102	35.5 (27)	27/20	35.9 (26)	101	26/50	36.1 (26)	102	26/50	30.7 (35)	98	35/50	
104	36 4 (23)	93/50	35.8 (25)	×	25/50	_	85	25/50	31 1 (35)	χ Υ	25/50	

## TABLE C 3

BODY WEIGHT CHANGES: MALE

SIGNI NO. : VOSS ANIMAL : MOUSE BEDZFI/Crlj[Crj:BDF1] UNIT : R REPORT TYPE : AI 104 SEX : MALE	[Cr.j:BDF1]		BODY WELGHT CHANGES ALL ANIMALS	(SUMMARY)			PAGE : 1
Group Name	Administration week 0	week	2	es.	77	rs.	
Control	23.3 ± 0.9	24. 2 ± 1. 1	24.7.± 1.7	25.3± 1.9	26.4土 1.4	27.0± 1.8	$27.5\pm\ 2.1$
250 ppm	23.3 ± 0.9	24.1± 1.3	24.8± 1.8	25.3± 2.0	26.1± 2.7	27.0 ± 2.2	27.9± 2.6
1000 ppm	23.3 ± 0.9	24.1± 1.1	25.0 ± 0.9	25.5± 1.2	26.2± 1.3	27.0± 1.4	27.6± 1.5
4000 չերու	23.3 ± 1.0	23.4± 1.2**	24.1± 1.6	24.8 ± 1.5	25.6± 1.3**	26.2± 1.2**	26.3± 1.2**
Significant difference ;	* : P ≤ 0.05	**: P ≤ 0.01		Test of Dunnett			

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ANTALA AND THE TOTAL OF T							PAGE : 2
Group Name	Administration week.	week 8	G.	10	1,1	12	13
Control	28.2 \(\pi\) 2.3	28.8 ± 2.4	29.2 = 3.0	$30.2\pm2.9$	30.4± 2.5	$31.9\pm2.4$	32.5土 2.5
250 ppm	28.8士 2.7	29.7± 2.2	30.2± 2.6	$31.2\pm 2.6$	31.3± 2.6	32.4± 2.9	33.1+ 2.9
1000 ppm	28.2± 1.7	28.6± 1.9	29.0± 2.9	30.3± 2.1	30.6± 2.2	31.7± 2.3	32.3± 2.5
4000 ppm	27.0± 1.3**	26.9± 1.5**	27.4± 2.2**	28.0± 1.3**	27.8± 1.7**	28.8± 1.8**	29.1± 2.2**
Significant difference;	*: P ≤ 0.05	** : P ≤ 0.01		Test of Dunnett		A A Company of the Co	

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KEFOKT 1YPE : AI 104 SEX : MALE							PAGE:
Group Name	Administration week. 14	week18	22	26	30	34	38
Control	32.9± 2.4	35.5± 2.8	$37.7 \pm 3.5$	39.9± 3.9	41.7± 4.3	43.2± 4.5	45.0± 4.7
250 ppm	33.6± 3.0	36.4± 3.4	39.1± 4.1	41.8± 4.6*	43.9± 4.7*	45.6± 4.5*	47.2± 4.2*
1000 ppm	32.8± 2.6	35.0± 3.2	37.4± 3.5	39.4± 4.1	41.2± 4.4	$43.0 \pm 4.7$	44.8± 4.7
4000 չրրա	29.4± 2.0**	30.9± 2.0**	32.2 ± 2.3**	32.9± 3.0**	34.0± 3.0**	34.9士 3.3**	35.9± 3.5**
Significant difference :	\ \ \ \ \ \ \ \ \ \	10 0 VI		Test of Dunnett			

KETOKI IYTE: AI 104 SEX: MALE	and the second s				10 (204.04/07) and a second se	THE REPORT OF THE PROPERTY OF	PAGE:
Group Name	Administration week,	week46	50	54	58	62	99
Control	46.7 ± 4.4	48.2± 4.3	48.5± 4.7	49.9± 4.1	49.9士 3.7	50.7- 4.2	51.6土 4.0
250 ppm	48.9± 4.2*	50.4± 3.9*	50.6 ± 4.0	52.4± 3.4**	52.3± 3.3**	52.6± 3.9	53.2 ± 4.4
mdd 0001	46.6± 4.9	47.7± 4.7	48.1± 5.4	50.5± 4.4	50.5± 4.4	$50.7 \pm 4.7$	51.4± 5.8
4006 թչու	36.9± 4.1**	37.8± 4.9**	38.7 ± 4.5**	40.3± 5.3**	40.4± 5.6**	40.6± 6.2**	41.2± 6.7**
		· ·		4 4			

Control         51.9±         4.9         52.2±         4.4         52.8±         4.6         52.2±         5.7         52.4±         5.9           250 ppm         53.3±         5.4         52.9±         6.5         53.4±         6.9         51.3±         9.4         54.2±         6.5           1000 ppm         52.6±         6.2         53.4±         5.8         53.5±         6.9         54.0±         6.5         54.2±         6.4           4000 ppm         42.3±         6.8**         43.4±         7.2**         44.5±         7.7**         42.9±         9.2**         42.8±         7.9***	REPORT TYPE : AI 104 SEX : MALE							PAGE :
53.3± 5.4 52.2± 4.4 52.8± 4.6 52.2± 5.7 52.4± 53.3± 5.4 52.9± 6.5 53.4± 6.9 51.3± 9.4 54.2± 52.6± 6.2 53.4± 5.8 53.5± 6.9 54.0± 6.5 54.2± 42.3± 6.8** 43.4± 7.2** 44.5± 7.7** 42.9± 9.2** 42.8±	ip Name	Administration 70		78	88	98	06	94
53.3± 5.4 52.9± 6.5 53.4± 6.9 51.3± 9.4 54.2±  52.6± 6.2 53.4± 5.8 53.5± 6.9 54.0± 6.5 54.2±  42.3± 6.8** 43.4± 7.2** 44.5± 7.7** 42.9± 9.2** 42.8±							$52.8\pm5.2$	50.7± 8.4
52.6± 6.2 53.4± 5.8 53.5± 6.9 54.0± 6.5 54.2± 42.3± 6.8** 43.4± 7.2** 44.5± 7.7** 42.9± 9.2** 42.8±							53.9± 7.2	53.2± 7.6
42.3± 6.8** 43.4± 7.2** 44.5± 7.7** 42.9± 9.2** 42.8±							52.8± 7.4	$51.7 \pm 8.0$
		42.3± 6.8**			42.9± 9.2**	42.8	43.0± 7.7**	40.7 ± 9.0**
Significant difference ; *: P $\leq$ 0.05 **: P $\leq$ 0.01			* : P ≤ 0.01		Test of Dunnett			

SIUNT NO. : UBSS ANIMAL : MOUSE BEDZF1/Crl;[Cr.j:BDF1] UNIT : R REPORT TYPE : A1 104 SEX : MALE	[Cr.j:BDF1]		BODY WEIGHT CHANGES ALL ANIMALS	(SUMMARY) PAGE: 6
Group Name	Administration week	on week		
	86	102	104	
Control	51.3 = 7.0	50.9± 7.2	50.6 ± 8.1	
250 ppm	53.3± 7.4	51.5± 8.7	49.7 = 9.4	
1000 ppm	50.7± 8.8	$49.0\pm9.6$	48.8± 9.2	
4000 չւրտ	41.7± 7.7**	41.0± 7.8**	38.9± 8.1≉	
Significant difference;	* : P ≤ 0.05	** : P ≤ 0.01		Test of Dunnett
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## TABLE C 4

BODY WEIGHT CHANGES: FEMALE

SEX : FEMALE		A STATE OF THE STA		PRINTERPROPORTION AND AND AND AND AND AND AND AND AND AN	en el este este el este este este este est	ARTO ARTO LONG CONTRACTOR AND ARTON	PAGE :
oroup ivane	Administration week 0	n week.	62	3	4	5	9
Control	19.0 ± 0.8	$19.3\pm1.1$	19.8 🛨 1.2	20.3 ± 1.0	20.7 ± 1.0	21.2 = 1.0	$21.7 \pm 1.2$
250 ppm	19.0 ± 0.8	19.4± 0.8	19.8± 1.0	20.4± 1.0	20.8± 1.0	21.3± 1.1	21.8± 1.3
1000 ppm	19.0± 0.8	19.5± 1.0	19.7 ± 1.4	$20.2 \pm 1.1$	20.9± 1.3	21.5± 1.6	21.6± 1.4
4000 թւթա	19.0± 0.8	19.3± 0.9	19.5 ± 1.0	20.1± 0.9	20.7± 0.9	21.0± 1.1	21.5± 0.9
Significant difference;	* : P ≤ 0.05	* <b>‡</b> : P ≤ 0.01		Test of Dunnett			

NELOKI 1175 - A1 104 SEX : FEMALE	AND				***************************************	THE RESIDENCE OF THE PROPERTY	PAGE :
Group Name	Administration week	n week 8	6	01	111	12	13
Control	$22.1\pm1.1$	22.7± 1.4	22.8 ± 1.4	22.9± 1.3	23.5± 1.3	23.9± 1.6	23.9土 1.8
250 ppm	22.3 ± 1.2	$22.6 \pm 1.3$	22.9± 1.4	23.2± 1.6	23.2± 1.4	23.9± 1.6	$24.2 \pm 1.9$
1000 ppm	22.1± 1.3	22.5± 1.5	22.6± 1.8	23.1± 1.7	23.2± 1.6	23.7± 1.6	24.0± 1.8
4000 ppm	21.9± 1.1	22.3± 1.1	22.4± 1.0	22.9± 1.1	23.0± 1.2	23.2± 1.3	23.5± 1.3
Significant difference;	* : P ≤ 0.05	* \$ 0.01		Test of Dunnett			

Group Name Administration week						PAGE :
14	, sek	22	3.6	30	34	88
Control 24.3± 1.8	25.8± 2.2	$27.6\pm3.2$	28.7± 3.3	30.2士 3.4	31.9± 3.8	33.1± 3.8
$250~\mathrm{ppm}$ $24.2\pm~2.0$	26.0± 2.3	27.9± 2.8	29.4± 3.0	30.8± 3.4	32.7± 3.6	33.8± 4.3
1000 ppm 24.4± 1.8	25.6± 2.0	27.0± 2.5	28.7± 3.2	29.8± 3.3	31.4± 3.4	32.3+ 3.8
4000 ppm 23.7± 1.3	24.6± 1.4**	25.7± 1.6**	26.6± 1.9**	27.1 ± 2.0**	27.9± 2.0**	28.6± 2.2₩
Significant difference ; * : $P \leq 0.05$ **	** : P ≤ 0.01		Test of Dunnett			

Group Name	Administration wood	Joon				T ADMINISTRATION OF THE PROPERTY OF THE PROPER	rage : 10
	42	46	20	54	58	62	99
Control	33.8± 4.1	34.6± 4.5	35.3 = 4.4	36.8 - 4.5	36.8 ± 4.5	36.8 ± 4.5	37.1± 4.4
250 ppm	34.2. 4.0	35.3± 4.2	35.6± 4.5	36.9± 4.9	36.7± 5.0	36.9± 5.2	37.4± 4.9
1000 ppm	33.0 = 3.7	33.9士 3.7	$33.9 \pm 4.2$	$35.4\pm 4.1$	35.5士 4.3	35.9± 4.5	36.0± 5.2
4000 ppm	29.0± 2.2**	29.1 ± 2.5**	29.6± 2.6*	30.4± 2.6≉*	30.8± 3.4**	30.9± 3.1**	31.2± 3.0**
Significant difference :	* : P ≤ 0.05	** : P ≤ 0.01		Test of Dunnett			

STUDY NO.: 0685 ANIMAL: MOUSE BGDZF1/Crlj[Crj:BDF1] UNIT: R REPORT TYPE: A1 104 SEX: FEMALE	[[Cr.j:BDF1]		BODY WEIGHT CHANGES (SUMMARY) ALL ANIMALS	(SUMMARY)			PAGE: 11
Group Name	Administration week 70	on week. 74	78	85	98	06	94
Control	38.0 ± 4.7	37.9± 4.7	38.4± 4.9	38.3± 5.0	37.8土 4.9	38.0 ± 4.7	37.5± 4.6
250 ppm	38.1± 5.4	37.4± 5.7	37.7± 5.8	37.4± 5.8	$38.1\pm 5.7$	37.6± 5.9	37.6± 5.5
1000 ppm	36.6± 5.8	36.5± 5.4	$36.9\pm5.2$	$37.2\pm5.0$	$37.2\pm5.2$	37.4± 5.5	36.4± 5.5
4000 มุมพ	31.3± 3.1**	31.4± 3.1**	31.4± 3.1**	31.5± 3.3**	31.4土 3.6**	31.6± 3.4**	31.8± 3.3**
Significant difference ;	. P № 8.	* * * * * * * * * * * * * * * * * * *		Test of Dunnett			

(HAN260)

Group Name         Administration week         102         10A           Control         36.2± 4.8         35.5± 5.2         36.4± 4.7           250 ppm         37.4± 5.6         35.9± 5.9         35.8± 5.7           1000 ppm         36.2± 5.2         36.1± 5.6         35.7± 5.0           4000 ppm         31.8± 3.9±         30.7± 4.0+         31.1± 4.3+           Significant difference:         *:P ≤ 0.05         **:P ≤ 0.01	ANJAAL : MOUSE DEDZEL/CRIJCKRISDET UNIT : R REPORT TYPE : AI 104 SEX : FEMALE	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		all animals	PAGE : 12
$36.2\pm 4.8$ $35.5\pm 5.2$ $36.4\pm 4.7$ $37.4\pm 5.6$ $35.9\pm 5.9$ $35.8\pm 5.7$ $36.2\pm 5.2$ $36.1\pm 5.6$ $35.7\pm 5.0$ $31.8\pm 3.9**$ $30.7\pm 4.0**$ $31.1\pm 4.3**$	оир Маве	Administration 98		104	
$36.2\pm$ $4.8$ $35.5\pm$ $5.2$ $36.4\pm$ $4.7$ $37.4\pm$ $5.6$ $35.9\pm$ $5.9$ $35.8\pm$ $5.7$ $36.2\pm$ $5.2$ $36.1\pm$ $5.6$ $35.7\pm$ $5.0$ $31.8\pm$ $3.9**$ $30.7\pm$ $4.0**$ $31.1\pm$ $4.3**$				K 0.7	
$37.4\pm 5.6$ $35.9\pm 5.9$ $35.8\pm 5.7$ $36.2\pm 5.2$ $36.1\pm 5.6$ $35.7\pm 5.0$ $31.8\pm 3.9**$ $30.7\pm 4.0**$ $31.1\pm 4.3**$	Control	36.2± 4.8	5.	$36.4\pm 4.7$	
$36.2\pm5.2$ $36.1\pm5.6$ $35.7\pm5.0$ $31.8\pm3.9**$ $30.7\pm4.0**$ $31.1\pm4.3**$ $*: P \le 0.05$ **: $P \le 0.01$	250 ррт				
31.8± 3.9** 30.7± 4.0** 31.1± 4.3** * : P ≤ 0.05 ** : P ≤ 0.01	1000 ppm		വ		
*: P ≤ 0.05 **: P ≤ 0.01	4000 թ.թ.ու	31.8± 3.9**		31.1± 4.3**	
*: P ≤ 0.05 **: P ≤ 0.01					
	Significant difference ;		** : P ≤ 0.01		Test of Dunnett

#### TABLE D 1

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS: MALE

(B10040)

MEAN FOOD CONSUMPTION (FC) AND SURVIVAL

STUDY NO. : 0685
ANIMAL : MOUSE B6DZF1/Crlj[Crj:BDF1]
UNIT : R
REPORT TYPE : A1 104
SEX : MALE

PAGE : 1

	Av. FC.	No. of	Av. FC.	% of	No. of	Av. FC.	% of	No. of	Av. FC.	Jo %	No. of
Week on Study		Surviv. (50>		cont. <50>	Surviv.		cont. (50)	Surviv.		cont. <50>	Surviv.
	4.1 (50)		4.0 (50)	86	50/50	4.0 (50)	86	50/50	3.9 (50)	95	50/50
	3.7 (50		3.8 (50)	103	50/50	3.8 (50)	103	20/20	3.9 (50)	105	50/50
	3.7 (50)	_	3, 7 (50)	100	50/50	3.8 (50)	103	20/20	3.7 (50)	100	20/20
	3.9 (49)	Ċ	3.9 (49)	100	20/20	3.9 (50)	100	20/20	3.9 (50)	100	50/50
	4.0 (49)	_	3.9 (49)	86	49/50	4.0 (50)	100	20/20	4.0 (50)	100	50/50
	4.0 (49)		4.0 (47)	100	49/50	3.9 (50)	86	20/20	3.9 (50)	86	50/50
	4.0 (49)	) 49/20	4.0 (49)	100	49/50	3.9 (49)	86	50/50	4.0 (50)	100	50/50
	4.1 (49)	) 49/50	4.2 (48)	102	48/50	3.9 (49)	95	50/50	3.9 (50)	92	50/50
	4.0 (49)	Ċ	4.1 (48)	103	48/50	4.0 (50)	100	20/20	4.0 (50)	100	50/50
	4.2 (49)		4.3 (48)	102	48/50	4.4 (50)	105	50/50	4.1 (50)	86	50/50
	4.1 (48)	ĺ	4.1 (48)	100	48/50	4.2 (50)	102	20/20	4.0 (50)	86	50/50
	4.2 (48)		4.2 (48)	100	48/50	4.1 (50)	86	50/50	4.1 (50)	86	50/50
	4.2 (48)		4.2 (48)	100	48/50	4.2 (50)	100	20/20	_	95	50/50
	4.2 (48)	_	_	100	48/50	4.2 (49)	100	20/20	_	86	50/50
	4.4 (48)		4.4 (48)	100	48/20	4.3 (50)	86	20/20	_	86	49/50
	4.3 (48)		_	105	48/50	4.4 (50)	102	20/20	4.3 (49)	100	49/50
	_	() 48/50	_	102	48/50	4.4 (50)	100	20/20	_	95	49/50
	_		4.5 (48)	100	48/50	4.3 (50)	96	20/20	_	93	49/50
	4.5 (48)	() 48/50	_	100	48/50	4.4 (50)	86	20/20	4.3 (49)	96	49/50
	_		4.7 (48)	100	48/50	4.6 (50)	86	50/50	4.7 (48)	100	48/50
	4.7 (48)		_	102	48/50	4.7 (50)	100	20/20	4.6 (47)	86	47/50
	4.7 (48)		_	102	48/50	4.5 (50)	96	20/20	4.6 (43)	86	47/50
	_	0 47/50	_	96	48/50	4.5 (50)	96	20/20	4.4 (42)	94	45/50
	_		_	102	48/50	4.7 (48)	102	48/50	4.7 (44)	102	45/50
	_	Ĺ	_	102	48/50	4.7 (48)	100	48/50	_	100	44/50
	_	_		107	48/50	4.6 (48)	100	48/50	_	100	44/50
	4.8 (45)		4.9 (47)	102	47/50	4.8 (48)	100	48/50	4.7 (42)	86	42/50
	_			107	47/50	4.9 (45)	107	46/50	_	104	40/50
	4.7 (45)	•	4.8 (46)	102	46/50	4.8 (43)	102	44/50	_	106	37/50
	4.8 (45)	_		100	44/50	4.9 (44)	102	44/50	_	86	34/50
	4.6 (44)	() 44/50	4.7 (42)	102	42/50	4.8 (41)	104	41/50	_	107	34/50
	5.0 (42)	_	_	86	34/50	5.0 (39)	100	39/50	_	102	28/50
	4.8 (40)	) 40/50	5.0 (34)	104	34/50	4.8 (39)	100	39/20	4.6 (23)	96	23/50
	4.6 (39)	) 39/20	4.7 (32)	102	32/50	4.8 (35)	104	35/50	4.4 (23)	96	23/50
86	4.9 (34)		5.2 (30)	106	30/20	5.0 (33)	102	33/50	5.2 (19)	901	19/50
	4.9 (32)	32/20	_	100	29/50	1.8 (30)	86	32/50	4.4 (17)	06	17/50
	4.7 (30)		_	86	29/50	4.6 (29)	86	29/50	4, 7 (15)	100	16/50

#### TABLE D 2

FOOD CONSUMPTION CHANGES AND SURVIVAL ANIMAL NUMBERS: FEMALE

(BI0040)

MEAN FOOD CONSUMPTION (FC) AND SURVIVAL

PAGE: 2

	MOUSE BGD2F1/Crlj[Crj:BDF1]			
21	SE		A1 104	EMALE
0685	Ş	øť	VI	Ξ
٠.	٠.		٠.	
.0.			REPORT TYPE	
×	ΛĽ		RT	
STUDY NO.	ANIMAL	UNIT	EP0	SEX
S	2	5	22	S

Av. FC. Week on Study											
ək Study		No. of	Av. FC.	% of	No. of	Av. FC.	% of	No. of	Av. FC.	% of	No. of
	Sur (50)	Surviv. <50>		cont. (50)	Surviv.		cont. (50)	Surviv.		cont. <50>	Surviv.
1 3.	(20)	50/50	3.7 (50)	103	50/50	3.7 (50)	103	50/50	3.6 (50)	100	50/50
	(20)	0/20	3.4 (50)	26	20/20	3.3 (50)	94	50/50	3.4 (50)	97	50/50
3.:	3 (50) 5	0/20	3.5 (50)	106	20/20	4	103	50/50	3.4 (50)	103	20/20
4 3.	_	0/20	3.6 (50)	103	20/20	3.6 (50)	103	50/50	ري ما	100	50/50
		0/20	9	100	50/50	3.6 (50)	100	50/50	3.5 (48)	26	50/50
6 3.0		0/20	9	100	20/20	3.6 (50)	100	50/50	2	97	50/50
7 3.	7 (50) 5	20/20	3.7 (50)	100	50/50	~	100	50/50	9	97	50/50
3.:		0/20	8	001	20/20	3.8 (50)	001	50/50	<b>!</b> ~	97	50/50
9 3.		0/20	3.8 (50)	103	20/20	3.8 (50)	103	50/50	_	97	50/50
10 3.		0/20	Ċυ.	103	50/50	4.0 (50)	105	50/50	3.9 (50)	103	50/50
11 3.		0/20	3.9 (50)	100	50/50	3.8 (50)	26	50/50		95	50/50
12 3.		0/20	6	105	50/50	3.7 (50)	100	50/50	3.7 (50)	100	50/50
13 3.		0/20	3.9 (49)	103	20/20	3.9 (50)	103	50/50	3.8 (50)	100	50/50
	9 (50)	0/20	3.8 (50)	26	50/50	3.9 (50)	100	50/50	_	97	50/50
18 4.0	0 (20)	0/20	0	001	50/50	3.8 (50)	92	50/50	-	86	50/50
	(20)	0/20	_	102	20/20		86	20/20	-	86	50/50
	(20)	0/20	~	108	20/20	4.2 (50)	108	20/20	_	801	50/50
	(49)	9/20	_	102	20/20		001	49/50	4.0 (50)	86	50/50
	(49)	9/20	_	105	20/20	4.1 (49)	86	49/50	_	86	50/50
	(49)	9/20	_	105	20/20		100	49/50	_	86	50/50
4.	(49)	9/20	4.6 (50)	102	20/20		00 1	49/50	4.3 (50)	96	50/50
4.		9/20	4.4 (50)	105	20/20	4.5 (47)	107	49/50	_	102	50/50
50 1.	(46)	9/20	_	102	49/50		105	19/20	4.6 (50)	105	50/50
4.	(48)	8/20	4.3 (49)	100	49/50	_	102	49/50	4.1 (50)	92	50/50
4.		1/20	4.4 (48)	102	48/50	-	707	49/50	_	001	50/50
4.	(41)	1/20	4.5 (48)	102	48/50		105	48/50	4.3 (49)	86 86	49/50
4.	(41)	2/20	4.4 (48)	102	48/50	4.6 (47)	107	47/50	4.4 (49)	102	49/50
4.	_	1/20	4.3 (46)	100	46/50	-	100	47/50	_	86	48/50
74 4.	_	2/20	4.4 (43)	102	43/50	-	102	46/50	4.3 (46)	001	47/50
78 4.		2/50	_	86	42/50	-	102	44/50	_	96	46/50
92 4.	_	0/20	4.5(41)	105	41/50	_	102	44/50	4.3 (45)	001	45/50
86 4.		37/20	4.6 (40)	105	40/20	4.6 (39)	105	39/20	4.4 (45)	001	45/50
90 4.	_	4/50	4.5 (37)	107	37/20	_	110	36/20	4.6 (42)	011	42/50
94 4.	.,	32/50	4.5 (34)	001	34/50	4.9 (29)	109	30/20	4.7 (41)	104	41/50
98 4.	_	0/20	4.5 (30)	110	30/20	_	112	29/20	4.4 (41)	107	41/50
02 4.	_	27/50	4.5 (25)	102	26/50	_	109	26/50	4.7 (34)	107	35/50
104 4. (	6 (23) 2:	23/50	4.5 (25)	86	25/50	4.6 (25)	100	25/50	4.4 (35)	96	35/50

## TABLE D 3

FOOD CONSUMPTION CHANGES: MALE

Group Name	Administration week	wook		***************************************				. dob
Victoria de la constanta de la	1	2	co	4	w	9	7	
Control	4.1 - 0.3	3.7-1-0.5	$3.7\pm0.5$	3.9 - 0.5	4.0 1 0.4	4.0 ± 0.4	4.0 ± 0.4	
250 ppm	4.0 + 0.4	3.8 \( \) 0.6	3.7士 0.6	3.9± 0.6	3.9± 0.6	4.0 ₹ 0.5	4.0± 0.4	
1000 mdd 0001	4.0 ± 0.4	3.8± 0.3	3.8 ± 0.4	3.9± 0.3	4.0± 0.3	3.9± 0.4	3.9± 0.4	
4000 թբու	3.9± 0.5**	3.9+ 0.5	3.7 = 0.4	3.9± 0.3	4.0± 0.3	3.9± 0.4	4.0± 0.3	
Significant difference;	P 0.05	** P N 0.01		Test of Dunnett				

REPORT TYPE : AI 104 SEX : MALE							PAGE :
Group Name	Administration week 8	week 9	10	11	12	13	14
Control	4.1士 0.5	4.0 ± 0.6	4.2 - 0.6	4.1-	4.2 ± 0.4	4.2± 0.3	4.2 ± 0.4
250 ppm	4.2 \pm 0.4	4.1± 0.5	4.3 ± 0.5	4.1± 0.4	4.2± 0.5	4.2± 0.4	4.2± 0.5
1000 ppm	3.9 ± 0.5	4.0± 0.5	4.4± 0.6	4.2± 0.3	$4.1\pm0.4$	4.2± 0.3	4.2± 0.3
4000 րդոռ	3.9 ± 0.4	4.0 = 0.4	4.1 ± 0.3*	4.0 ± 0.4	4.1± 0.5	4.0 ± 0.5	4.1
Significant difference;	* : P ≤ 0.05	**: P ≤ 0.01		Test of Dunnett			

				e de desente de la constitución de company de desente de la constitución de constitución de company de la cons			
Group Name	Administration week 18	reek 22	26	30	34	38	42
Control	$4.4\pm0.4$	4.3 ± 0.5	4.4 0.4	$4.5\pm0.6$	4.5± 0.6	4.7 1 0.7	4.7 ± 0.6
250 ppm	4.4± 0.4	4.5± 0.4	<b>4.5</b> ± 0.4	4.5± 0.5	4.5 ± 0.5	4.7± 0.4	4.8± 0.6
1000 ppm	4.3 ± 0.4	4.4± 0.4	4.4 0.5	4.3± 0.5	4.4± 0.5	4.6± 0.4	4.7 ± 0.4
4000 թրա	4.3 ± 0.5	4.3 ± 0.4	4.2 ± 0.6	4.2± 0.4**	4.3 ± 0.4*	4.7 ± 0.6	4.6± 0.5
Significant difference ;	*:P≤0.05 **	**: P ≤ 0.01		Test of Dunnett			

STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Crl,[Cr.:BDF1] UNIT : R REPORT TYPE : A1 104 SEX : MALE	Cr.j:BDF1]	Pt Al	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	ES (SUMMARY)			PAGE: 4
Group Name	Administration week. 46	week. 50	54	58	69	99	70
Control	4.7± 0.5	4.7± 0.6	4.6 ± 0.8	4.7± 0.6	4.6± 0.5	4.8± 0.4	4.6± 0.6
250 ppm	4.8 = 0.5	4.5 ± 0.9	4.7 = 0.4	4.8 ± 0.4	4.9± 0.5*	4.9± 0.6	4.9士 0.4
1000 ррт	4.5 ± 0.7	4.5 = 0.8	$4.7\pm$ 0.5	4.7 ± 0.6	4.6± 0.8	4.8± 0.7	4.9± 0.6
4000 թվյա	4.6土 0.7	4.4± 0.6	4.7 = 0.6	4.7± 0.7	4.6± 0.7	$4.7 \pm 0.5$	<b>4.8</b> ± 0.6
Significant difference;	*	** : ₽ ≤ 0.01		Test of Dunnett			

(HAN260)

BAIS 4

PAGE:						
	86	4.9. <u>1</u> 0.6	5.2 ± 0.6	5.0± 0.6	5.2± 0.7	
	94	4.6 ± 1.1	4.7± 0.9	4.8± 0.8	4.4 ± 0.9	
	06	4.8 - 0.7	5.0 + 0.8	<b>4.</b> 8± 0.8	4.6± 0.8	
S (SUMMARY)	98	5.0 ± 0.7	4.9士 0.7	5.0 ± 0.7	5.1± 0.9	
FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	78	$4.6 \pm 0.9$	4.7± 1.2	4.8± 0.8	4.9 ± 0.8	
FG AL	week 78	4.8 - 0.6	4.8 ± 0.6	4.9± 0.5	4.7± 0.9	
i[Cr.j:BDF1.]	Administration week 74	4.7 - 0.7	4.8 + 0.8	4.8 ± 0.6	5.0 ± 1.0	
STUDY NO.: 0685 ANIMAL: MOUSE B6D2F1/Crl,i[Cr.j:BDF1] UNIT: R REFORT TYPE: A1 104 SEX: MALE	Group Name	Control	250 թթա	1000 ppm	4000 չերու	

Test of Dunnett

\*\*: P ≤ 0.01

Significant difference ; \* \* :  $P \le 0.05$ 

(HAN260)

PAGE: 6						
FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS						
	on week	2 O ÷ 7 L		4.6± 0.9	4.6± 0.8	4.7± 1.1
STUDY NO. : 0685  ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]  UNIT : R  REPORT TYPE : A1 104  SEX : MALE	Administration week. 102	8 0 + 0 8	0.0	4.9 1.0	4.8± 0.6	4.4士 0.9
STUDY NO. : 068 ANIMAL : MOU UNIT : R REPORT TYPE : A SEX : MALE	Group Name	(on tro	1010	250 ррм	1000 ppm	4000 լորու

Test of Dunnett	BAIS 4
Significant difference ; * : P $\leq$ 0.05 ** : P $\leq$ 0.01	(HAN260)

# TABLE D 4

FOOD CONSUMPTION CHANGES: FEMALE

KELOKI 117'E : AI 104 SEX : FEMALE							PAGE :
Group Name	Administration week I	week 2	3	4	2	9	2
							Address and the second
Control	3.6 ± 0.3	3.5± 0.4	3.3 = 0.3	3.5± 0.2	3.6± 0.3	3.6± 0.3	3.7± 0.3
250 ppm	3.7± 0.2	3.4± 0.3	3.5 ± 0.3*	3.6土 0.3	3.6± 0.3	3.6± 0.4	$3.7 \pm 0.2$
1000 ppm	3.7± 0.3	3.3± 0.4	3.4 0.3	3.6± 0.3	3.6± 0.5	3.6± 0.3	3.7± 0.3
4000 рүш	3.6± 0.4	3.4± 0.4	$3.4\pm 0.3$	3.5± 0.3	3.5± 0.4	3.5± 0.3	3.6± 0.3
Significant difference;	* : P ≤ 0.05	* : P ≤ 0.01		Test of Dunnett			

REFORT TYPE : AI 104 SEX : FEMALE							PAGE :
	Administration week. 8	week 9	01	11	12	13	14
	3.8± 0.3	$3.7\pm0.3$	3.8+ 0.3	3.9± 0.3	3.7± 0.4	3.8 ± 0.4	3.9士 0.3
	3.8± 0.3	3.8± 0.3	3.9 = 0.4	3.9± 0.3	$3.9 \pm 0.3$	3.9士 0.4	3.8± 0.4
	3.8± 0.4	3.8 ± 0.5	$4.0\pm0.4$	3.8± 0.3	$3.7 \pm 0.3$	3.9± 0.4	3.9± 0.4
	$3.7 \pm 0.3$	3.6± 0.4	3.9 0.3	3.7± 0.2	3.7± 0.3	3.8± 0.3	3.8± 0.3

Test of Dunnett

\*\*: P ≤ 0.01

Significant difference ; \* : P  $\leq$  0.05

(HAN260)

STUDY NO. : 0685 ANIMAL : MOUSE B6DZFL/Crlj[Crj:BDF1] UNIT : g REPORT TYPE : A1 104 SEX : FEMALE	[Cr.j:BDF1]	ii. 4	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	BS (SUMMARY)			PAGE : 9
Group Name	Administration week. 18	on week	36	30	34	38	42
Control	4.0 + 0.4	4.2± 0.6	3.9± 0.6	4.1± 0.5	4.2± 0.6	4.4.	4.5± 0.6
250 ppm	4.0± 0.5	4.3± 0.6	4.2± 0.7	4.2± 0.7			
под 0001	3.8+ 0.5	4.1± 0.5					
4000 main	3.9 ± 0.4	4.1+ 0.5	4.2± 0.6	4.0 ± 0.5			
Significant difference;	*: P ≤ 0.05	**: P ≤ 0.01		Test of Dunnett			
(HAN260)							BAIS 4

STUDY NO. : 0685 ANIMAL : MOUSE BEDZFI/Crlj[Crj:BDF1] UNIT : R REPORT TYPE : AI 104 SEX : FEMALE	-BDF1]	FOOD ALL A	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	UMMARY)			PAGE: 10
Group Name	Administration week						
***************************************	46	50	54	58	62	99	70
Control	4.2± 0.6	<b>4.</b> 4 ± 0. 7	4.3 ± 0.7	4.3± 0.7	4.4 1 0.7	4.3± 0.6	4.3 1 0.7
250 ppm	<b>4.4</b> ± 0.8	4.5士 0.7	4.3± 0.8	4.4± 0.8	4.5 = 0.7	4.4	4.3± 0.6
1000 ppm	4.5 ± 0.7	<b>4.</b> 6± 0.6	4.4± 0.6	4.4± 0.7	4.6± 0.5	4.6± 0.8	4.3± 0.8
4000 չւրտ	4.3± 0.5	4.6± 0.8	4.1 ± 0.6	4.3± 0.6	4.3 ± 0.6	4.4 ± 0.5	4.2± 0.5

Test of Dunnett

\*\*: P ≤ 0.01

Significant difference ; \* : P  $\leq$  0.05

(HAN260)

STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Cr1;[Cr.j:BDF1] UNIT : R REPORT TYPE : A1 104 SEX : FEMALE	1:30F1]	Pi Asi	FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	S (SUMMARY)			
Group Name	Administration w	week 78	82	98	06	94	86
Control	4.3 ± 0.6	4.5± 0.7	4.3 ± 0.6	4.4± 0.6	4.2 1.0.7	4.5± 0.7	4.1± 0.8
250 ppm	4.4± 0.6	4.4土 0.6	4.5+ 0.8	4.6± 0.7	4.5± 0.9	4.5± 0.7	4.5 ± 0.6
1000 ppm	4.4± 0.8	4.6± 0.8	4.4± 0.8	4.6± 0.5	4.6± 0.8	4.9± 0.5	4.6± 0.8*

PAGE: 11

BAIS 4

 $4.4\pm 0.6$ 

 $4.7\pm 0.6$ 

 $4.6\pm0.7$ 

4.4 ± 0.8

 $4.3 \pm 0.6$ 

 $4.3\pm 0.5$ 

4.3 ± 0.5

4000 µm

42

PAGE : 12						
FOOD CONSUMPTION CHANGES (SUMMARY) ALL ANIMALS	k 104	4.6 ± 0.8	4.5士 0.6	4.6± 0.9	4.4± 0.7	
-1.j[Cr.j:BDF1]	Administration week 102	4.4± 1.3	4.5+	4.8± 0.7	4.7± 0.9	
STUDY NO. : 0685 ANTMAL : MOUSE BEDZF1/Crlj[Cr.j:BDF1] UNIT : R REPORT TYPE : A1 104 SEX : FEMALE	Group Name	Control	250 ppm	1000 ppm	4000 ppm	

Test of Dunnett

\*\* : P ≤ 0.01

# TABLE E 1

CHEMICAL INTAKE CHANGES: MALE

PAGE: 1	**************************************					
2			0	4	11	39
		2	∓0	32 H	140±	∓669
			0	φ	12	48
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	9	+0	3€‡	142土	∓885
			0	4.	10	38
		വ	+ 0	36±	148±	€14±
	7000		0	4	10	46
(SUMMARY)		4	∓0	37±	149±	∓609
CHANGES			0	4	11	54
CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	**************************************	т	0 <del>1.</del>	37.±	148±	∓665
AI CE			0	4	10	73
	Administration (weeks)	2	- <del>-</del> -  0	38∓	153±	655 ±
	tration		0	m	11	22
/crl;[cr.j:BDFt] y	Adminis	<u> </u>	∓0	42 <b>±</b>	∓ 291	∓ 299
STUDY NO.: 0685 ANIMAL : MOUSE BGDZF1/Cr1,[Cr.j:BDF1] UNIT : ng/kg/day REPORT TYPE : A1 104 SEX : MALE	Group Name		Control	250 ppm	1000 ppm	4000 չորու

9	CHEMICAL INTAKE		CHANGES	(SUMMARY)
•	ALL ANTMALS	V.		

Administration (weeks) 9 10 11 12 12 13 14 14 15 15 15 15 15 15 15 15 15 15 15 15 15	STUDY NO. : 0685  ANTAAL : MOUSE BEDZF1/CrljfCrj;BDF1] UNIT : mg/kg/d a y  REPORT TYPE : AI 104  SEX : MALE	Cr.j:BDF1]			CHEA	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)							PAGE :
0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0         0±         0±         0         0±         0±         0         0±         <	Group Name	Administ 8	tration (w	eeks)		01			THE RESIDENCE OF THE PARTY OF T	12		13		14	
35±     3     4     34±     4     33±     3     4     32±     3       137±     12     138±     12     145±     20     138±     10     131±     12     131±     11     127±       1     582±     50     583±     45     586±     45     577±     45     562±     54     556±     47     557±	Control	<del>.</del>	0	<del>-</del> 0	0	÷! 0	0	<del>+</del> 0	0	#0	0	÷ 0	0	+ 0	0
$137 \pm 12 \qquad 138 \pm 12 \qquad 145 \pm 20 \qquad 138 \pm 10 \qquad 131 \pm 12 \qquad 131 \pm 11 \qquad 127 \pm 282 \pm 50 \qquad 583 \pm 45 \qquad 586 \pm 45 \qquad 577 \pm 45 \qquad 562 \pm 54 \qquad 556 \pm 47 \qquad 557 \pm 287 $	250 ppm	35+	m	34±	4	34.±	4	33∓	es	33 +	4	32∓	m	31.	4
$582\pm$ 50 $583\pm$ 45 $586\pm$ 45 $577\pm$ 45 $562\pm$ 54 $556\pm$ 47 $557\pm$	mdd 0001	137±	12	138#	12	145±	50	138∓	10	131±	12	131±	11	127 ±	10
	4000 յւթյու	582±	20	583±	45	于989	45	577±	45	∓299	54	∓999	47	₹29	56

	42
	38
	34
(SUMMARY)	30
CHEMICAL INTAKE CHANGES ALL ANIMALS	26
	(weeks)
1/Crlj[Crj:BDF1] a y	Group Name Administration (weeks) 30 34 38 42
STUDY NO. : 0685 ANIMAL : MOUSE B6D2FL/Crlj[Cr.j:BDF1] UNIT : ng/kg/day REPORT TYPE : A1 104 SEX : MALE	Group Name

***************************************	18	18 22	22		26		30		34	Made in the second seco	38		42	
Control	÷I 0	0	÷I	0	+0	0	<del>- </del> 0	0	<del>T</del> 0	0	<del></del> -0	0	÷0	0
250 ppm	30∓	e	∓67	ო	27±	က	79°	rs	52±	က	722±	m	725 ±	m
1000 ppm	123±	13	117±	10	112±	11	105 ±	12	104±	10	105 ±	111	$102\pm$	10
4000 ppm	558±	99	537±	52	513±	29	494±	45	488±	42	522±	92	498 ±	50

. INTAKE CHANGES (SUMMARY)	ALS
CHEMICAL	ALL ANIMALS

STUDY NO.: 0685
ANIMAL: MOUSE BGDZFI/Crlj[Crj;BDFl]
UNIT: mg/kg/day
REPORT TYPE: Al 104
SEX: MALE

PAGE: 4

Group Name	Administ	Administration (weeks)	(s)	***************************************									100	
	46		20		54		58		62		99		70	
Control	÷ 0	0	+0	0	<del>†</del> 0	0	+0	0	÷-1	0	<del>∵</del> 0	0	干0	0
250 ppm	24+	2	22+	4	22 +	23	23.+	83	24+	ო	23+	က	23+	ಣ
1000 ppm	76	15	94±	15	76 ±	12	94±	12	∓26	16	<del>+</del> 26	22	+26	20
4000 բւրու	700€	108	464∓	09	469 ±	63	470±	99	457±	87	469十	97	461±	85

(HAN300)

		86
		94
		06
(SUMMARY)		86
STUDY NO.: 0685  ANIMAL : MOUSE BGBZFI/Crli[Crj:BDF1]  ALL ANIMALS  UNIT : mg/kg/d a y  REPORT TYPE : Al 104  SEX : MALE		82
	(weeks)	78
Crl;[Crj:BDFl] /	Administration	74
STUDY NO. : 0685 ANIMAL : MOUSE B6D2FL/Crl;[Crj:BDF1] UNIT : mg/kg/day REPORT TYPE : Al 104 SEX : MALE	Group Name	

PAGE: 5

74 78 82				***************************************	-					***************************************		
	78	82		98		06		94		86		
					And Andrews of the Andrews							
Control $0\pm$ 0 $0\pm$ 0 $0\pm$ 0 $0\pm$ 0			0	+1 0	0	+0	0	+ 0	0	<del> </del> 0	0	
250 ppm $23\pm$ 4 $23\pm$ 6			9	23+	4	$23\pm$	ಎ	75. + 27.	വ	25 +	4	
1000 ppm $90\pm~11$ $94\pm~21$ $88\pm~13$			13	93±	12	91±	15	94#	15	103土	28	
4000 ppm 460± 73 435± 76 472± 114			114	485土	106	436±	86	453 ±	134	512	66	

(HAN300)

PAGE: 6

CHEMICAL INTAKE CHANGES (SUMMARY)
ALL ANIMALS

STUDY NO. : 0685
ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1]
UNIT : mg/kg/d a y
REPORT TYPE : Al 104
SEX : MALE

Group Name	Administ	Administration (weeks)	eks)	
**************************************	102		104	
Control	∓0	0	+10	0
250 ppm	23+	rc	24∓	(Q
	+ 00	20	+ 80	
mdd ooyy	-	ā t	-  	0.0
4000 ppm	443 ±	107	489 ±	153

50

(HAN300)

# TABLE E 2

CHEMICAL INTAKE CHANGES: FEMALE

S	HEMICAL	INTAKE	CHANGES	(SUMMARY)
W	ALL ANIMALS	TS		

CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANTMALS PAGE : 7	eeks) 2 3 4 5 6 7	0  op 0	$43\pm$ 3 $43\pm$ 3 $43\pm$ 3 $42\pm$ 2	$168\pm$ 16 $166\pm$ 15 $170\pm$ 12 $166\pm$ 16 $165\pm$ 13 $167\pm$ 11	
	Administration (weeks)			168±	+902
STUDY NO. : 0685 ANIMAL : MOUSE B6DZF1/Crlj[Crj:BDF1] UNIT : mg/kg/d a y REPORT TYPE : Al 104 SEX : FBMALE	Administratic 1	0 ∓0 .	48±	190± 13	753+ 28
STUDY NO. : 0685 ANIMAL : MOUS. UNIT : mg_/i REPORT TYPE : A1 SEX : FBMALE	Group Name	Control	250 ppm	1000 ррп	4000

STUDY NO.: 0685 ANIMAL: MOUSE B6D2F1/Cr1;[Cr.j:BDF1] UNIT: ng/kg/day REPORT TYPE: A1 104 SEX: FEMALE	:BDF1]			CHBA	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)	•						PAGE
Group Name	Administr 8	Administration (weeks)	reeks)		01		11	AND	12		13		14	
Control	     0	0	· 0	0	<del> </del>	0	<del>†</del> ]	0	÷I 0	0	∓0	0	+0	0
250 ppm	42 ±	ю	41=	ო	42±	4	42+	က	41 ±	63	40+	4	40+	ಣ
1000 ppm	167±	14	T991	18	172±	14	∓691	12	158±	13	<del>+</del> 191	14	161 ±	15
4000 չդրու	∓ +999	56	651±	69	<del>+</del> 289	49	648 ±	42	637±	51	€40±	45	644 ±	52

	Group Name Administration (weeks)
(SUMMARY)	
CHEMICAL INTAKE CHANGES ALL ANIMALS	
	ion (weeks)
STUDY NO. : 0685 AVIMAL : MOUSE B6DZF1/Crlj[Crj:BDF1] UNIT : mg/kg/d a y REPORT TYPE : Al 104 SEX : FEMALE	Administration
STUDY NO. : 0685 ANIMAL : MOUSE BEDZFL/Cr UNIT : mg/kg/day REPORT TYPE : AI 104 SEX : FEMALE	Group Name

SEX : FEMALE														PAGE: 9
Group Name	Administ	ration (	weeks)						The second secon	-	900000 Acad acad (management)			
	81		18 22		26		30		34	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	38		42	
Control	÷I	0	÷ 0	0	<del></del> 0	0	<del></del>	0	T-0	0	<del>-</del> 0	0	÷  0	0
250 ppm	+: 88 8	ጥ	39∓	が	36+	2	34+	9	34+	ເດ	34+	വ	34#	വ
1000 ppm	148±	19	153土	20	148±	27	137±	18	133±	61	136±	20	137±	23
4000 բրոո	∓689	29	642 ±	29	634±	06	$\pm 297 \pm$	29	∓069	63	∓809	16	∓069	69

STUDY NO.: 0685  ANTMAL : MOUSE B6D2F1/Cr1;[Crj:BDF1] UNIT : mg/kg/day  REPORT TYPE : A1 104  SEX : FBMALE	:j:BDF1]			CHEMICAL INT ALL ANIMALS	CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	CHANGES	(SUMMARY)							PAGE: 10
Group Name	Administration (weeks)	ation (	weeks)		54	4	58		29		99		0.2	
Control	÷ 0	0	+0	0	<del>4</del>   0	0	+1 0	0	<del> </del>   	0	<del>∓</del> 0	0	- <del> </del> 0	0
250 ppm	31.	9	32±	7	79 ∓	ιo	30#	9	31+	ર	30∓	ø	767	Ø
1000 ррт	134±	23	138±	23	124±	18	125±	19	131±	18	$129 \pm$	24	119±	24
4000 руян	∓689	19	∓819	100	545±	. 92	±858	92	∓ €99	99	$\mp 992$	28	537±	49

	Administration of the second o	0
	86	#0
	TO THE PERSON AND AND ADDRESS OF THE PERSON AND ADDRESS OF THE PERSON ADDRESS OF T	0
	94	∓0
	***************************************	0
	06	+0
	111001110	0
(SUMMARY)	98	<del>+ </del> 0
CHANGES		0
CHEMICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS	82	+10
J 44		0
	(weeks) 78	÷ 0
	Administration 74	0
2F1/Cr1;[Crj:BDF1] 1 a y	Adminis 74	÷-0
STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1] UNIT : mg/kg/d a y REPORT TYPE : A1 104 SEX : FEMALE	Group Name	Control

MIS 4	
B	
(AN300)	
≅	

80

554土

92

 $\mp 969$ 

101

 $\pm 83 \pm$ 

103

 $\pm 693$ 

64

 $542\pm$ 

19

555±

26

 $545\pm$ 

4000 ppm

 $127\,\pm$ 

19

136±

22

 $124\pm$ 

17

 $124 \pm$ 

23

 $121\,\pm$ 

22

 $126\pm$ 

20

 $120\,\pm$ 

1000 ppm

30∓

250 ppm

31+

30∓

30+

UMMARY) PAGE						
CHENICAL INTAKE CHANGES (SUMMARY) ALL ANIMALS		0	9	23	102	
	(weeks)	- <del></del> 0	32+	129±	570±	
:BDF1]	Administration (weeks)_ 102	0 +0	31.± 9	134± 14	610± 123	
STUDY NO.: 0685 ANUMAL : MOUSE B6D2F1/Cr1;[Cr;:BDF1] UNIT : mg/kg/day REPORT TYPE : A1 104 SEX : FEMALE	Group Name	Control	250 ppm	1000 ppm	4000 յրջու	

# TABLE F 1

HEMATOLOGY: MALE

STUDY NO. : 0685 ANIMAL : MOUSE BEDZFI/Crij[Crj:BDF1] WEASURE. TIME : 1	3 B6D2F1/Cr1j l	[Cr.j:BDF1]			HEM	HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	JMMARY) (05W)								
SEX : MALE	REPORT	REPORT TYPE : AI													PAGE :
Group Name	NO. of Animals	RED BLOOD CELL 1 O⁵ ∕ µℓ	CELL	HEMOGLOBIN R/dl	BIN	HEMATOCRIT %	CRIT	MCV f &		MCH P.R		MCIIC R/dl		PLATELET 1 0³/µl	T g
Control	30	9.74 ± 1.	1.07	13.7 ±	1.1	42. 4 <u>±</u>	3.1	43.7-1-	2.1	14.2 -	8.0	32. 4 ==	0.7	1674±	465
250 ppm	28	9.15± 1.	I. 48	13.2+	1.9	40.8±	5.5**	44.8±	2.0	14.5+	0.7*	32.4±	1.5	1804±	486
1000 ppm	28	7.47± 1.	1,15**	12.6±	1.9**	33.4±	4.5**	45.2±	4.3	17.0±	1. 4**	37.6±	2. 4**	1758±	319
4000 ppm	15	5.48± L	I. 42**	10.5+	2.8**	27.7±	4. 4**	52.4±	9.3**	19.2+	0.8**	37.7±	6.7**	1957±	675
Significant	Hilference;	Significant difference ; * : P ≤ 0.05		**: P ≤ 0.01				Test of Dunnett	nett						

PAGE: 2						BAIS 4
HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	OBIN	0.1	0. 4**	0. 7***	2.2*	Test of Dunnett
	METHEMOCLOBIN	0.4⊹	1.0+	2.6+	5.3+	** : P \square 0.01
FL/Crlj[Crj:BDFL] REPORT TYPE : Al	RETICULOCYTE %	2.5± 1.2	3.8± 2.9**	4.8± 5.0**	1.8+ 2.6	* : P ≤ 0.05
5 SE B6D2F1/Cr1,j 1 REPORT	NO. of Animals	30	28	28	15	Significant difference ;
STUDY NO. : 0685 ANIMAL : MOUSE BGDZFL/Cĸlj[Crj:BDFl] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	Group Name	Control	250 ppm	1000 mpm	4000 ppm	Significant (HCL070)

STUDY NO.: 0685 ANIMAL : MOUSE B6D2F1/Cr1;[Crj:BDF1] MEASURE. TIME : 1 SEX : MALE REPORT TYPE : A1	SS ISE B6D2F1/Cr1. 1 REPORT	PF1/Cr1;[Crj:BDF1] REPORT TYPE : A1	_			HEMATOLOC ALL ANIMA	HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	Q								PAGE: 3
Group Name	NO. of Animals	ΨΒC 1 O³ ∕ μℓ	יק	Dif NEUTRO	Differential WDC (%)	WBC (% LYMPHO		MONO		EOSINO		BAS0		OTHER		
Control	30	4. 90 ⊹	3. 03	30 -⊦	14	<del>4</del> €9	16	4 +	~	+I &		· <del>+I</del> 0	0	\frac{1}{k}	_	
250 ppm	28	4.77±	2.57	29+	14	€4±	14	e †	-	3+	63	+0	0	0 十		
1000 ppm	28	5.76±	2.52	5e±	[4	∓49	16	4+		3 +1	m	#0	0	10	0	
4000 ppm	15	5.42±	2.35	39.	21	25±	17	2+	23	5+	-	+1	0	<del>+</del> i		
Significant	Significant difference : *: P ≤ 0.05	 ∗	0.05	**: P S 0.01	0.01			Test	Test of Dunnett	1,					10 TO THE TOTAL	

# TABLE F 2

HEMATOLOGY: FEMALE

STUDY NO. : 0685 ANIMAL : MOUSE BGDZF1/Crlj[Crj:BDF1] MEASURE TIME : 1	3 B6D2F1/Crlj	[Cr.j:BDF1]			HE	HEMATOLOCY (SUMMARY) ALL ANIMALS (105W)	UMMARY) 105W)								
SEX : FEMALE	KEI'OKI	KEPORT TYPE : A1													PAGE :
Group Name	NO. of Animals	RED BLC 1 O <sup>5</sup> / µ	RED BLOOD CELL 1 O <sup>s</sup> /µl	HEMOGLOBIN g/dl	BIN	HEMATOCRIT	CRIT	MCV f 2		MCII p.g		MCHC R / dl		PLATELET 1 0³∕µℓ	1
	M		And Anticked by November 1		Management of the second										April Artificial management of the state of
Control	83	10.01±	0.43	14.5 =	0.7	44.2±	2.6	44.1±	L.3	14.5±	0.5	32.8±	0.7	±1711	235
250 ppm	25	9.05∓	1.15**	13. 4±	1. 2**	41.1±	3. 3**	45.6±	2.0**	14.8+	0.6**	32.5±	0.8	1043±	317
1000 ppm	24	7.46±	1. 44**	12.0±	2. 2**	34.5±	5.0**	47.1±	5.1**	16.2±	0.8**	34.6±	2. 6**	∓996	383
4000 ppm	34	5.97±	1. 17**	II. 2±	2. 2**	29.9∓	3. 9**	51.1±	6.7**	18.8±	1. 3**	37.1±	4. 1**	1124±	358
Significant o	Significant difference; *:P ≤ 0.05	0 ⋈ d : *		# : P ≤ 0.0I	I			Test of Dunnett	nett						

	PAGE: 5						
HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)		METHEMOGLOBIN %	$0.4\pm$ 0.1	0.7± 0.2**	2.0± 0.6**	4.0± 1.5**	**: P \le 0.01 Test of Dunnett
Cr.j:BDF1]	IPE : AI	RETICULOCYTE %	$2.1\pm0.6$	4.0± 1.9**	7.0± 5.7**	3.6+ 4.5	
E B6D2F1/Crlj[C	REPORT TYPE : A1	NO. of Animals	23	25	24	34	Significant difference; *: P ≤ 0.05
STUDY NO. : 0685 ANIMAL : MOUSE B6DZFI/Crlj[Crj:BDF1] MEASURE. TIME : 1	SEX : FEMALE	Group Name	Control	250 ppm	1000 ppm	4000 ppm	Significant o

STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Crl;[Crj:DBF1] MEASURE TIME : 1 SEY : FRIMALE	55 ISE B6D2F1/Cr. 1	Lj[Crj:BDF1				HEMATOLOC ALL ANIMA	HEMATOLOGY (SUMMARY) ALL ANIMALS (105W)	S								
Group Name	NO. of Animals	WBC 103/µl	Sut.	Diff	erential	Differential WBC (%)		MONO		EOSINO		BASO		OTHER		PAGE: 6
Control	23	3.04±	1. 23	21±	Ħ	+89	12	3+	63	4-1-	<i>w</i> .	<del></del> 0	0	- <del></del> [	-	
250 թթա	25	3.91+	3.81	23 <sup>±</sup>	σ,	±01	01	3+	٦	+i &	63	+10	0	+	-	
1000 ppm	24	3.40+	1.88	797	13	€5 ±	91	<b>4</b>	4	3+	63	†1	0	+1	4	
4000 ppm	34	13.05± 42.81	42.81	30+	16	+19	17	4	\$ <b>±</b>	3 +	*	+! 0	1	2±	69	
Significant	Significant difference; *: P ≤ 0.05	*	≤ 0.05	** \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\	0.01			Test	Test of Dunnett							

# TABLE G 1

BIOCHEMISTRY: MALE

STUDY NO. : 0685 ANIAAL : MOUSE B6DZF1/Crlj[Crj:BDF1] MEASURE. TIME : 1 SEX : MALE	B6D2F1/Crlj	BF1/Crlj[Crj:BDF1] REPORT TYPE : A1			BIC ALI	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (1054)	(SUMMARY) 105W)								PAGE ::
Group Name	NO. of Animals	TOTAL F g / dl	TOTAL PROTEIN R / dl	ALBUMIN R / d2	N	A/G RATIO	LIO	T-BILIRUBIN mg/de	RUBIN	GLUCOSE mg/dk		T-CHOLESTEROL mg/dl	TEROL	TRIGLYCERIDE mg/dl	RIDE
Control	30	5.3 :-	0.7	2.6 ±	0.4	1.0 =	0.2	0.11 =	0.02	185 ⊹	37	114±	55	52 ±	25
250 ppm	28	5.6±	6.0	2.8±	0.4	1.1+	0.2	0.12±	0.01*	188±	27	148±	82	70∓	44
1000 ppm	27	5.1+	0.7	2.5±	0.4	1. 0 ±	0.2	∓91.0	0.07**	182±	44	122±	29	64±	38
4000 ppm	15	5.1±	0.8	2.5	0.5	1.0±	0.2	0.21±	0.08**	∓691	46	117±	43	+ 29 +	36
Significant difference ; * : P ≤ 0.05	lifference ;	Vil ≃ *	0.05	** : P ≤ 0.01	01			Test of Dunnetl	nnetl						

(HCL074)

STUDY NO. : 0685 ANIMAL : MOUSE B6DZF1/Cr1,i[Cr.j:BDF1] MEASURE, TIME : 1	; B6D2F1/Crl,i	[Cr.j:BDF1]			BI AI	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	SUMMARY) 05W)									
SEX : MALE		REPORT TYPE : A1													PAGE :	
Group Name	NO. of Animals	PHOSPHOLIPID mg/d2	OL IP ID	AST I U / 2	8	ALT I U / 2		LDII	6	ALP I U / L	5	G-GTP I U / L		CK I U / &	g	
Control	30	199-	73	101	136	57 ±	78	298-1	236	208 ☆	69	<del>!</del>	1	53	27	
250 ppm	28	245 ±	103	73±	45	58±	72	250±	145	227 ±	116	+1	Т	42±	11	
1000 ppm	27	214±	103	93+	82	52±	53	297±	143	251±	218	<del>+!</del>		10±	70	
4000 ppm	15	∓961	49	147±	138	81 <del>+</del>	601	∓019	344**	703 ∓	112	+	-	124 ±	261	
Significant difference ; * : P ≤ 0.05	ifference ;	* : P ≤ 0	), 05	**: P ≤ 0.01				Test of Dunnett	nett							1

(HCL074)

Group Name NO. of UREA NITROGEN Animals ms/dt			ALL	ALL ANIMALS (105W)	54)							. 10,40
	TROGEN	SODIUM m Eq / &		POTASSIUM mEq∕2	W	CHLORIDE m Eq / &		CALCIUM mg/dl		INORGAN mg/d2	INORGANIC PHOSPHORUS	
Control 30 $22.3\pm$	8.6	153±	67	4. 2 十	0.3	121	m	9.0 -	0,6	6.3±	6.0	
250 ppm 28 21.9±	9. 9.	152±	_	4. 1±	0.3	120+	cs.	$9.2 \pm$	0.7	5.9±	0.6	
1000 ppm $27$ $22.3\pm$	8.2	153±	6)	4.4+	0.4	121±	ო	8.9	0.6	6.2+	1.1	
4000 ppm 15 25.1±	7.3	153±	23	4.4+	0.4	121	rs	8.8	0.7	$6.2 \pm$	0.9	
Significant difference; *: P ≤ 0.05		**: P ≤ 0.01			=	Test of Dunnett	ett					

# TABLE G 2

BIOCHEMISTRY: FEMALE

STUDY NO. : 0685 ANIMAL : MOUSE B6DZF1/Crlj[Crj:BDF1] MEASURE, TIME : 1	g BGDZF1/Crlj	[Cr.j:BDF1]			BIOC	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	(SUMMARY) (OSW)								
SEX : FEMALE		REPORT TYPE : A1													PAGE:
Group Name	NO. of Animals	TOTAL PROTEIN g/dl	ROTEIN	ALBUMIN g/dl		A/G RATIO	LIO	T-BILIRUBIN mg/dl	RUBIN	GLUCOSE mg/dl		T-CHOLESTEROL mg/dl	STEROL	TRIGLYCERIDE mg/d&	SRIDE
Control	53	4.9±	0.4	2.6⊹	0.2	1.14	0.2	0.11 🕂	0.02	154±	30	75±	11	40±	15
250 ppm	25	4.9	0.6	2.7±	0.3	L. 2±	0.2	0.12±	0.04	155#	23	†1 88	58	51,4	27
mad 0007	24	4.9±	8.0	2.6±	0.4	1.2+	0.3	0.15±	0.05**	155±	23	81+	25	799	21
4000 ppm	34	5.5	I. 0**	2.9+	0. 4**	1.2+	0.3	$0.22\pm$	0.09**	144±	38	+96	49	<del>+</del> 02	41
Significant	Significant difference; *: P ≤ 0.05	0 ∨I 	1, 05	**: P ≤ 0.01				Test of Dunnett	mett						

(HCL074)

STUDY NO.: 0685 ANIMAL : MOUSE B6D2F1/Crlj[Crj:BDF1] MEASURE. TIME : 1 SEX : FEMALE	B6D2F1/Crlj	[Crj:BDF1] TYPE : A1			B3	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	SUMMARY) .05W)								PAGE .	ر.
Group Name	NO. of Animals	PHOSPHOLIPID mg/dl	LIPID	AST I U / g	6	ALT I U / g	g g	LDil I U / g	e	ALP I U / g	ê	G-GTP I U / g		CK I U / g	!	
Control	23	135 🚉	26	122	177	54.±	7.1	736±	221	∓698	146	<del>+</del> I 0	-	<del>- </del> 69	64	
250 ppm	25	760 +	103	117±	143	£65	201	223±	144	370±	187	<b>1</b>	-	54±	30	
1000 ppm	24	148±	39	81±	36	31±	16	282±	203	232±	104**	+0	0	∓89	56	
4000 ppm	34	174±	75**	136±	124	44±	20	542±	622**	<del></del>	113	+1	က	82±	56	
Significant c	Significant difference ; *: P ≤ 0.05	* . P S 0.		** : P ≤ 0.01	_			Test of Dunnett	mett							

(HCL074)

STUDY ND. : 0685 ANIMAL : MOUSE BEDZFI/Crlj[Crj:BDF1] MEASURE. TIME : 1	6 B6D2F1/Cr1j 1	[Cr.j:BDF1]			BIC	BIOCHEMISTRY (SUMMARY) ALL ANIMALS (105W)	SUMMARY) 05W)							
SEX : FEMALE	REPORT	REPORT TYPE : AL											PAGE :	9
Group Name	NO. of Animals	UREA NI mg/d&	UREA NITROGEN mg/dk	SODIUM m Eq∕2		POTASSIUM m.Eq./ &	î Wn	CHLORIDE m Eq / 2		CALCIUM mg/dl		INORGAN mg/dl	INORGANIC PHOSPHORUS	
Control	23	16.2±	2.6	151±	63	4.0	0.3	121 ±	69	8.7±	0.4	5.4±	0.8	
250 ppm	25	17.6±	5.4	152±	83	4.2	0.4	122±	က	8.9±	0.5	5.9	1.1	
1000 ppm	24	17.7±	4.9	151±	က	4.3+	0.5	121 ±	m	9.0+	0.7	6.3	J. 0**	
4000 ppm	34	23.9±	23.9± 16.0**	154±	** 3**	4.4	0.8	122±	44	9.3	<b>%**</b> 0.7**	6.5+	J. 6**	
Significant o	Significant difference; *: P ≤ 0.05	0 ≥ q · *		**: P ≤ 0.01			1	Test of Dunnett	att:					

(HCL074)

# TABLE H 1

URINALYSIS: MALE

#### Urinalysis of male mice

In the dosed groups, ketone body could not be measured by urine test paper in some animals, because their urine were colored by metabolite of test substance.

The inspection items and number of animals that could not be measured are shown as followed.

Ketone body: 1000 ppm(2), 4000 ppm(14)

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

STUDY NO. : 0685	ORINALYSIS	
ANIMAL : MOUSE BO	5E B6D2F1/Cr1;[Crj:BDF1]	
MEASURE. TIME: 1		
SEX : MALE	REPORT TYPE : A1	

SEX : MALE	REPORT TYPE : A1	YPE : /	A1											PAGE: 1	
Group Name	NO. of Animals	pII5.0	6.0	5.0 6.0 6.5 7.0 7.5 8.0	7.0.7	.5 8.		8.5 CIII	Protein ± + 2+ 3+ 4+ CHI	Glucose	IID	Netone body - ± + 2+ 3+ 4+ CHI	0ccult blood - ± + 2+ 3+	IID	
Control	31	0	23	4	s	8	0 6		0 0 16 13 2 0	31 0 0 0 0 0		4 22 5 0 0 0	28 1 0 1 1		
250 ppm	29	0	ಣ	ဘ	2	7	3 1		0 2 17 9 1 0	29 0 0 0 0 0		4 24 1 0 0 0	29 0 0 0 0		
1000 ppm	28	0	rc	rs	6	, ,	2 0		0 3 19 6 0 0	28 0 0 0 0 0		5 17 4 0 0 0	26 0 0 0 2		
4000 ppm	16	0	က	က	23	ıs.	3 0		137410	16 0 0 0 0 0		0 1 1 0 0 0 ?	16 0 0 0 0		
Significant	Significant difference :		*: P \leq 0.05	0.05	***************************************	# : P \	≥ 0.01			Test of CHI SQUARE					

<sup>? :</sup> Significant test is not applied, because No. of data in this group is less than 3.

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(HCL101)

SEX : MALE REPORT TYPE : A1	MEI OM I I I				PAGE: 2
Group Name NO. Anji	NO. of Animals	Urobilinogen ± + 2+ 3+ 4+ CHI			
Control ;	31	31 0 0 0 0			
250 ppm	29	29 0 0 0 0			
1000 ppm	28	28 0 0 0 0			
4000 ppm	16	16 0 0 0 0			
Significant difference :		*: P ≤ 0.05 **	# : P ≤ 0.01	Test of CMI SQUARE	

# TABLE H 2

URINALYSIS: FEMALE

#### Urinalysis of female mice

In the dosed groups, ketone body could not be measured by urine test paper in some animals, because their urine were colored by metabolite of test substance.

The inspection items and number of animals that could not be measured are shown as followed.

Ketone body: 1000 ppm(2), 4000 ppm(26)

Group Name	NO. of Animals	pll 5.0 6.0		6.5 7.0 7.5		8.0 8.5 C	CIII –	Protein	Glucose — ± + 2+ 3+ 4+ CIII	Ketone body  - ± + 2+ 3+ 4+ GII	Occult blood - ± + 2+ 3+ CIII
								Management of the control of the con		And a second sec	
Control	24	0 1	e	က	10 7	0 2	0	1 17 6 0 0	24 0 0 0 0 0	9141000	20 0 0 0 4
250 ppm	25	0 0	63	4	13 5	5 1	0	2 15 8 0 0	25 0 0 0 0 0	5 19 1 0 0 0	23 0 0 2 0 *
1000 ppm	26	0 4	63	4	6	0 2	0	4 18 4 0 0	26 0 0 0 0 0	9 15 0 0 0 0	23 0 0 2 1
4000 ppm	35	0 13	63	4.	11 5	5 0	0	7 26 2 0 0 *	35 0 0 0 0 0	180000	35 0 0 0 0 *
Significant	Significant difference ;	٠٠ *	*: P ≤ 0.05		ط  #	## : P ≤ 0.01		Test	Test of CHI SQUARE		

STUDY NO. : 0685 ANHAL : MOUSE BED2F1/Cr1;[Cr.j:BDF1] SEX : FEMALE : 1 SEX : FEMALE : 1 SEvoup Name
B6D2F1/C REPC NO. of Animals 21 25 26 35

## TABLE J 1

ORGAN WEIGHT, ABSOLUTE: MALE

	EYS		0.091	0.078	1.020	0.065	
	KIDNEYS	A CONTRACTOR OF THE PROPERTY O	0.645土	0.620±	0.812±	0.624±	
			0.048	0.186	0.191	0.206	
	LUNGS		0.196±	0.235±	0.250±	0.250±	
	***************************************		0.018	0.022	0.025	0.039**	
0	IIEART		0, 225 ±	0.231±	0.238±	0.255±	
TE (SUMMAR) 547)	SS		0.028	0.032	0.212	0.023	
ORCAN WEIGHT:ABSOLUTE (SUMMARY) SURVIVAL ANIMALS (105W)	TESTES		0.218±	$0.212\pm$	0.270±	0.223±	
ORGAN A SURVIV	ALS		0.002	0.002	0.002	0.002	
	ADRENALS		0.009 ±	0.009	0.010±	₩ 00.00	
	eight		7.4	9.1	8. 2	7.5**	
.j:BDF1]	Body Weight		47.2 ± 7.4	47.2± 9.1	46.0± 8.2	36.8± 7.5*	
STUDY NO. : 0685 ANUMAL : MOUSE BGDZF1/Crlj[Crj;BDF1] REPORT TYPE : A1 SEX : MALE UNIT: g	NO. of Animals		30	28	28	15	
STUDY NO. : 0685 ANIMAL : MOUSE REPORT TYPE : A1 SEX : MALE UNIT: g	Group Name		Control	250 ppm	1000 ppm	4000 րլու	

PAGE: 1

(IICL040)

Significant difference ; \*: P  $\leq$  0.05 \*\*: P  $\leq$  0.01

BAIS 4

Test of Dunnett

(105W)	BRAIN	0.016	0.014*	0.013	0.012
ORGAN WEIGHT:ABSOLUTE (SUMMARY) SURVIVAL ANIMALS (105W)	BRA	0. 465 ±	0. 455土	0.462±	0.472±
50 tX	LIVER	1.765± 0.566	1.970± 0.777	1.821± 0.505	1.954± 0.476
	SPLEEN	0.111	0.048	0. 224**	0.480**
2F1/Cr1,[Cr.j:BDF1]		0.122土	3 0.118+	3 0.215±	5 0.353士
STUDY NO.: 0685 ANIMAL: MOUSE BEDZF1/Crlji REPORT TYPE: A1 SEX: MALE UNIT: g	Group Name NO. Anim	Control 30	250 ppm 28	1000 ppm 28	4000 ppm 15

PAGE: 2

Test of Dunnett	BAIS 4	
**: P ≤ 0.01	an manadalahan kangan kang	
*: P ≤ 0.05		
Significant difference;	(IICL040)	

# TABLE J 2

ORGAN WEIGHT, ABSOLUTE: FEMALE

					ž	ž
	EYS		0.053	0.065	0.284**	1. 092**
	KIDNEYS	Oddishing	$0.408\pm$	0.410±	$0.525\pm$	$0.640\pm$
	Ş		0.019	0.021	0.019*	0.051**
	LUNGS		0.171±	0.177±	0.182±	0.194±
	ST.		0.014	0.014	0.026*	0.021**
S	IIEART		0, 164 ±	0. 168±	0.182±	0.183±
JTE (SUMMARY 105W)	OVARIES		0.050	0. 171	0.173	0.055
ORCAN WEIGHT:ABSOLUTE (SUMMARY) SURVIVAL ANIMALS (105W)	0VA		0. 044 ±	0. 105±	0. 093 ±	0.045±
ORGAN W SURVIVA	ADRENALS		0.002	0. 002	0.002	0.002
	ADRI		0. 013 ±	0.013±	0. 013 ±	0.012±
	Weight		8.8	5. 8	5. 2	3. 9**
rj:BDF1]	Body		33.8⊥	33.5±	33.8±	28.6±
STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Cr1j[Crj:BDF1] REPORT TYPE : A1 SEX : FBMALE UNIT: g	NO. of Animals		23	25	24	34
STUDY NO. : 068. ANIMAL : MOUR REPORT TYPE : A. SEX : FEMALE UNIT: g	Group Name		Control	250 թթա	1000 ppm	4000 րրա

PAGE: 3

(HCL040)

BAIS 4

Test of Dunnett

\*\*: P ≤ 0.01

Significant difference ; \* : P  $\leq$  0.05

TUDY NO.	••	0685	
VIMAL	• •	MOUSE	B6D2F1/Cr1j[Cr.j:BDF1]

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

STUDY NO. : 0685
ANIMAL : MOUSE B
REFORT TYPE : A1
SEX : FEMALE
UNIT: 8

UNIT: g							PAGE: 4
Group Name	NO. of Animals	SPLEEN	Nati	LIVER	2	BRAIN	N
		MANAGE CONTRACTOR OF THE PARTY		A 444 was a second			
Control	23	$0.125\pm0.110$	0.110	1.419-	0.648	0.472± 0.013	0.013
250 ррт	25	0. 207.±	0.160**	1.557±	0.690	0.470+	0.012
1000 ppm	24	0.251±	0.181**	$1.827 \pm$	1.038**	0.477±	0.014
4000 չչչու	34	0.333±	0.453**	1.872±	1. 282**	0.474±	0.017

(HCL040)

BAIS 4

Test of Dunnett

**\***\* : P ≤ 0.01

Significant difference : \* :  $P \leq 0.05$ 

## TABLE K 1

ORGAN WEIGHT, RELATIVE: MALE

	MOLICE REPORT /Cwl : [Cw::-pner]
	BG B
0685	MOLECT

SEA : MALE UNIT: %								PACE : 1
Group Name	NO. of Animals	Body Weight (g)	ADREMALS	TESTES	IIEART	LUNGS	KIDNEYS	
Control	30	47.2-1.4	0.020± 0.005	0. 471 ± 0. 091	0.490 ± 0.101	$0.428\pm\ 0.145$	1.402± 0.327	
250 ppm	87	47.2± 9.1	0.020± 0.007	0.466± 0.117	0.511± 0.137	$0.580\pm\ 0.776$	$1.359\pm0.285$	
1000 ppm	88	46.0± 8.2	0.022± 0.007	0.604 ± 0.480	$0.534\pm0.123$	0.562± 0.446	$1.752\pm 1.908$	
4000 թթա	15	36.8± 7.5**	0.026土 0.008*	0.632± 0.157**	0.719± 0.174**	0.724± 0.667**	1.745± 0.304**	

(IICL042)

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SEX : MALE UNIT: %					PAGE: 2
Group Name	NO. of Animals	SPLEEN	LIVER	BRAIN	
Control	30	$0.275\pm0.272$	$3.848\pm1.590$	1.011± 0.189	
250 ppm	88	0.269± 0.159	4.652± 3.270	I. 006 ± 0. 236	
1000 ppm	88	0.483± 0.489**	$4.088 \pm 1.528$	1. $040\pm\ 0.214$	
4000 թբու	15	1.061 ± 1.541**	5.506± 1.795**	1.331 ± 0.265*	

(IICL042)

BAIS 4

# TABLE K 2

ORGAN WEIGHT, RELATIVE: FEMALE

	LUNGS KIDNEYS	$0.517 \pm 0.098$ $1.226 \pm 0.223$	0.542± 0.111 1.248± 0.228	0.548± 0.096 1.600± 1.017**	0. 686± 0. 178** 2. 179± 3. 411**
(4.)	HEART	0.490± 0.056	0.512± 0.071	0.543± 0.068*	0.653± 0.108**
OKGAN WEIGHT:RELATIVE (SUMMARY) SURVIVAL ANIMALS (105W)	OVARIES	$0.139 \pm 0.177$	$0.315\pm\ 0.496$	0.287± 0.543	0.158± 0.197
ORGAN W SURVIVA	ADRENALS	0.039 ± 0.006	0.039 ± 0.005	0.039± 0.007	0.043± 0.008
Cr.j:BDF1]	Body Weight (g)	33.8土 4.8	33.5± 5.8	33.8± 5.2	28.6土 3.9**
5 SE B6D2F1/Cr1;[ .1	NO. of Animals	23	25	24	34
STUDY NO.: 0685 ANIMAL : MOUSE B6D2F1/Cr1;[Cr.j:BDF1] REPORT TYPE : A1 SEX : FEMALE UNIT: %	Group Name	Control	250 ppm	1000 ppm	4000 ppm

PAGE: 3

(HCL042)

BAIS 4

Test of Dunnett

 $++ : P \le 0.01$ 

Significant difference ;  $\star$  : P  $\leq$  0.05

PAGE						
ORGAN WEIGHT:RELATIVE (SUMMARY) SURVIVAL ANIMALS (105%)	BRAIN	1. 423 ± 0. 197	1. 440± 0. 249	1. 440 ± 0. 202	1.688± 0.217**	Test of Dunnett
ORGAN # SURVIVA	LIVER	$4.302\pm\ 2.250$	4.789士 2.580	5.435± 2.856	6.365± 3.181*	P ≤ 0.01
.Cr.j:80F1.]	SPLEEN	0.376土 0.339	0.625± 0.475**	0.775土 0.583***	1.117± 1.189**	Significant difference ; * : P $\leq$ 0.05 **:
5 SE B6D2F1/Cr1,i[ L	NO. of Animals	23	25	24	34	difference ;
STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Crli[Cr.j:BDF1] REPORT TYPE : A1 SEX : FEMALE UNIT: %	Group Name	Control	250 ррт	1000 ррт	4000 րբու	Significant

(IICL042)

### TABLE L 1

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

MALE: ALL ANIMALS

ALL ANIMALS (0-105W)

STUDY NO. : 0685 ANIMAL : MOUSE REPORT TYPE : AI	: 0685 : MOUSE B6D2F1/Cr1j[Crj:BDF1] : A1	HISTOPATHOLOGICAL FI ALL ANIMALS (0-105W)	TCAL FINDINGS :NO (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)		
SEX	: MALE					PAGE :
Organ	Findings	Group Name No. of Animals on Study Grade (%) (%) (%)	Control 50 3 4 (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 2 4 (%) (%) (%) (%) (%)
(Integumentar	(Integumentary system/appandage)					
skin/app	ulcer		<50> 0 0 0 0 0 0 0 0	<pre></pre>	<50> 0 2 0 0 ( 0) ( 4) ( 0) ( 0)	<50> 0 1 0 ( 0) ( 2) ( 0) ( 0)
	erosion	(0)(0)	(0 ) (0 )			0 2 0 0 (0) (0) (0)
	inflammation	(0 ) (0 )	(0 ) (0 )		(0) (2) (0) (0)	
	squamous cell hyperplasia	1 0 ( 2) ( 0)	(0 ) (0 )		(0)(0)(0)(0)	
	scab	(0) (0)	(0 ) (0 )		3 2 0 0 (6) (6) (7) (0)	0 4 0 0 (0) (0) (0)
subcutis	inflammation	( 0) ( 2)	<50> 0 0 0 ( 0) ( 0)	<50> 0 0 0 0 ( 0) ( 0) ( 0)	<50> 0 2 0 0 ( 0) ( 4) ( 0) ( 0)	(6 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0 0
Respiratory system    nasal cavit	system) exudate	\$\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	(0 ) (0 ) (00) (00) (00)	<50> 0 0 0 0 ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 <05>	(6 ) (6 ) (6 ) (6 ) 0 0 0 0 0 0 0 0 0

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

(IIPT150)

\*\*: P ≤ 0.01 Test of Chi Square

(IIPT150)

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

STUDY NO. : 0685
ANIMAL : MOUSE BGD2F1/Cr1j[Crj:BDF1]
REPORT TYPE : A1

	Group Name No. of Animals on Study	Control 50	250 <b>µp</b> m 50	1000 ppm 50	000 50
Organ	Grade Findings		(%) (%) (%) (%)	(%) (%) (%)	(%) (%) (%) (%)
(Respiratory system)	system}				
nasal cavit	eosinophilic change:olfactory epithelium	<pre></pre>	<50> 11 0 0 0 ( 22) ( 0) ( 0) ( 0)	<50> 8 0 0 (16) (0) (0) (0)	<50> 2 0 0 0 0 ( 4) ( 0) ( 0) ( 0)
	eosinophilic change:respiratory epithelium	15 0 0 0 (30) (30) (30) (30) (30) (30) (30	16 6 1 0 <b>*</b> (32) (12) (2) (0)	13 1 0 0 (26) (26) (2) (0) (0)	8 2 0 0 (16) (4) (0) (0)
	respiratory metaplasia:olfactory epithelium	11 0 0 0 0 (22) (22) (0) (0) (0)	8 1 0 0 (16) (16) (16) (16) (16)	4 0 0 0 (8) (8) (9) (9)	2 0 0 0 ** ( 4) ( 0) ( 0) ( 0)
	respiratory metaplasia:gland	8 2 0 0 (16) (16) (19) (10)	9 4 0 0 (18) (18) (19) (19)	10 2 0 0 (20) (4) (0) (0)	4 0 0 0 (0) (0) (0)
	atrophy:olfactory epithelium	1 0 0 0 (2) (2) (3) (4) (5)			
паѕоріагупх	eosinophilic change	<pre></pre>	<50> 2 0 1 0 ( 4) ( 0) ( 2) ( 0)	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)	<50> 3 0 0 ( 6) ( 0) ( 0) ( 0)
larупх -	arthritis	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<250> 0 0 0 0 0 ( 0 ) ( 0 ) ( 0 )	(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 b	1: Slight 2: Moderate 3: Marked a Number of animals examined at the site b: Number of animals with lesion	4 : Severe			

(IIPT150)

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

STUDY NO. : 068 ANIMAL : MOL REPORT TYPE : A1 SEX : MAL	: 0685 : MOUSE BGDZF1/Cr1j[Crj:BDF1] : A1 : MALE		HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)	ICAL FIN 0-105W)	DINGS :NON-	NEOPLASTIC	CLESTON	S (SUMMARY)								PAGE	ო 
Organ	Findings	Group Name No. of Animals on Study Grade	22 (%)	Control 3 3 4 (%)	4 (%)	1 (%) (%)	250 ppm 50 2 3 (%) (%)	4 (%)	(%)	1000	1000 ppm 50 3 ) (%)	4 (%)	1 (%)	(3)	4000 ppm 50 3	4 (%)	
(Respiratory system)	system)																On the second se
lung	congestion		0 1 ( 0) ( 2)	<50> 0 ) ( 0) (	0 (0	2) (2	<50> 0 0 0) (0)	0 (0	0 (0 )	(50) ( ( 0) (	) (0 0 (0)	0 0	0 )	9	<50> (0) (0)	0 0	
	hemorrhage		0 1 (0) (2)	0 (0 )	0 0	0 0 0	0 0	6 )	1 (2)	2 (7	0 0 )	0 (0	0 0	1 (2)	0 0	00	
	squamous cell metaplasia		(0 ) (0 )	0 (0 )	0 6	0 0 0	0 (0 0)	0 )	0 )	0 0	0 0	0 0	, ,	0 0	0 (0	0 0	
	accumulation of foamy cells		1 0 ( 2) ( 0)	0 (0 )	0 6	0 0	0 0	0 )	0 )	o ô	0 0	0 0	00	00	0 0	0 0	
	bronchiolar-alveolar cell hyperplasia	ia	(0 ) (0 )	0 (0 )	0 0	3 (9 )	(O ) (O	o ()	0 (0 )	0 (0 )	0 (0 )	0 0	(2)	0 (0	0 )	0 0	
	uremic pneumonitis		(0 ) (0 )	0 (0 )	00	0 1 (0 )	1 0 2) (2)	0 0	0 (0	3 (9)	0 (0 )	0 0	2 (4)	7 ( 14)	0 0	0 )	** (
	accumulation:macrophage		(0) (0)	0 (0 )	0 6	2) (2)	(0 ) (0 0 0	o (i)	0 0	(2)	0 0 )	0 6	1 ( 2)	2 (4)	0 0	0 )	
	degeneration:blood vessel		(0 ) (0 )	0 (0 )	0 6	0 0 0	1 0 2) (2)	0 (0	0 0	(2)	0 0	o 6	1 (2)	2 (4)	0 )	0 )	
Grade 1 : Slight <a>&gt; a : Number b b : Number (c) c : b / a * Significant difference ;</a>	2 : Moderate of animals examined of animals with lesi 100 * : P ≦ 0.05	Marked .01	4 : Severe Test of Chi Square														

STUDY NO. : 0685 ANIMAL : MOUSE BGDZFL/Crlj[Crj:BDFl]

ANIMAL : MOUSE REPORT TYPE : A1 SEX : MALE

IC LESTONS (SUMMARY)

ALL ANIMALS (0-105W)

PAGE: 4 32 0 0 0 \*\* ( 64) ( 0) ( 0) ( 0) \* 0 0 00 4 % 00 00 00 000 10 0 0 0 (20) (20) (30) 0 0 0 0 0 0 0 0 0 1 0 (0) (0) (0) (0) 1 2 3 (%) (%) (%) 4000 **որտ** 50 36 2 (72) (4) ( \* 0 0 4 % 12 0 0 0 ( 24) ( 0) ( 0) ( 0) (0) (0) (0) (81) 2 0 0 0 ( 4) ( 0) ( 0) ( 0) (0)(0)(0)(0)(0) 00 00 0 (0 2 3 (%) (%) 100**0 ppm** 50 0 0 0 43 2 ( (86) (4) ( ( **-**|€ 41 1 0 0 \*\*\* ( 82) ( 2) ( 0) ( 0) 2 0 0 0 ( 0) ( 0) 0 1 0 0 (0) (0) (0) (0)(0)(0)(0)(0) 12 0 0 0 (24) (24) (30) (30) (30) 5 0 0 0 0 (10) (10) (10) 4 % 250 ppm 50 m 38 ~ § -188 2 3 4 (%) (%) (%) 10 0 0 0 (20) (20) (30) (30) 8 0 0 0 (01) 0 3 0 0 (0) (0) 0 1 0 0 (0) (0) (0) (0)(0)(0)(0)(0) 00 5 0 0 ( 10) ( 10) ( Control 50 Group Name No. of Animals on Study Grade granulopoiesis:increased increased hematopolesis deposit of hemosiderin lymphadenitis thrombus Findings atrophy atrophy (Hematopoietic system) bone marrow .ymph node thymus spleen

4 : Severe 3 : Marked Grado 1: Slight 2: Moderale 3: Ma < a > a: Number of animals examined at the site b b: Number of animals with lesion c: b / a \* 100 c: b / a \* 100 Significant difference : \*: P  $\leq$  0.05 \*\*: P  $\leq$  0.0

 $\star\star$ : P  $\leq$  0.01

Test of Chi Square

BAIS4

(HPT150)

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE

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

PAGE: 5

Organ	Findings	Group Name Control No. of Animals on Study 50 Grade 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 punn 50 1 2 3 4 (%) (%) (%) (%)	4000 ppm 50 x 4 x (%) (%) (%) (%)
(Hematopoietic system)	ic system)				
spleen	extramedullary hematopoiesis	<50> 16 4 0 0 ( 32) ( 8) ( 0) ( 0)	<50> 21 5 0 0 (42) (10) (0) (0)	<50> 16 17 1 0 ** ( 32) ( 34) ( 2) ( 0)	<pre></pre>
	engorgement of erythrocyte			1 0 0 0 (2) (3) (4) (4)	4 0 0 0 ( 8) ( 8) ( 9) ( 9)
	follicular hyperplasia	2 0 0 0 (4) (4) (6) (6) (6)	2 0 0 0 (4) (4) (6) (6) (6)		
(Circulatory system)	.system)				
lleart	thrombus	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<pre></pre>	<pre></pre>	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	mineralization	1 0 0 0 ( ) ( ) ( ) ( ) ( )	2 1 0 0 (4) (2) (0) (0)	4 0 0 0 (8) (8) (9) (9)	3 2 0 0 (6) (4) (0) (0)
	degeneration		(2) (0) (0) (0)	1 0 0 0 (2) (3) (4) (4)	(2) (0) (0) (0)
	myocardial fibrosis	(2) (0) (0) (0)	2 0 0 0 (4) (4) (6) (6)	1 0 0 0 (0) (0) (0)	
Grade	1: Slight 2: Moderate 3: 3 a: Number of animals examined at the site b: Number of animals with lesion	3 : Marked 4 : Sovere site			

BAIS4

(IIPT150)

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

(HPT150)

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

STUDY NO. : ANIMAL : REPORT TYPE : SEX :	STUDY NO. : 0685 ANIMAL : MOUSE B6D2F1/Cr1j[Crj:BDF1] REPORT TYPE : A1 SEX : MALE	HISTOPATHOLOGICAL FINDINGS :NA ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		PAGE : 6
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 µpm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Circulatory system) heart arte	system) arteritis	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 029	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(0) (0) (0) (0) (0)
(Digestive system) oral cavity sq	stem) squamous cell hyperplasia	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<020 0 0 0 0 0 0 0 0 0 0 0 0	<00> (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0
tooth	dysplasia	<50> 0 3 1 0 ( 0) ( 6) ( 2) ( 0)	<50> 1 1 1 0 ( 2) ( 2) ( 2) ( 0)	<50> 0 1 1 0 ( 0) ( 2) ( 2) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0
tongue	artoritis	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0 0 0 0	<50> 2 0 0 0 ( 4) ( 0) ( 0) ( 0)	<50> 0 0 0 0 ( 0) ( 0) ( 0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0
stomach	atrophy:glandular mucosa	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> (0) (0) (0) (0) (0)	<50> 0 0 0 0 0 ( 0) ( 0) ( 0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0
	hyperplasia:forestomach	6 0 0 0 0 (12) (13) (15) (15) (15) (15) (15)	3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	(2)(0)(0)(0)	(2) (0) (0) (0)

(IIPT150)

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

STUDY NO. : 068 ANIMAL : MOU. REPORT TYPE : A1 SEX : MAL.	: 0685 : MOUSE BGDZF1/Cr1j[Crj:BDF1] : A1 : MALE	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	c	
		THE STATE OF THE S			Wee .
Organ	Findings	Group Name Control  No. of Animals on Study 50  Grade 1 2 3 4  (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 µpm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%)
(I) i est i	(mo + e z				
(Digestive s	ystem)				
stomach	erosion:glandular stomach	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<pre></pre>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<pre></pre>
	ulcer:glandular stomach	(2) (0) (0) (0)			0 0 0 0 0
	hyperplasia:glandular stomach	8 0 0 0 0 (16) (16) (16) (16) (16) (16) (16) (16)	10 0 0 0 (20) (20) (30) (30)	8 0 0 0 0 (16) (16) (16) (16)	3 0 0 0 0 (9) (9)
small intes	inflammation	<0) (0) (0) (0) (0) (0) (0) (0) (0) (0) (	<pre></pre>	<0) (0) (0) (0) (0) (0) (0) (0) (0) (0) (	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)
liver	angioctasis	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> 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 0 0 0
	necrosis:central		0 1 0 0 (0) (0) (0) (0)	0 1 0 0 (0) (0) (0) (0)	(0)(0)(0)(0)
	necrosis:focal	2 0 0 0 ( 4) ( 4) ( 6) ( 6)	0 1 2 0 (0) (2) (4) (0)	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4 3 0 0 (8) (8) (9) (0)
Grade <a>&gt; b (c) Significant o</a>	Grade 1: Slight 2: Moderate 3: Mederate 4: Mederate 4: Mederate 4: Mederate 5: Mederate 5	3 : Marked 4 : Severe c silc P ≤ 0.01 Test of Chi Square			

40 0 0 0 \*\* ( 80) ( 0) ( 0) ( 0) 4000 ppm 50 m 38 1 0 0 (2) (2) (3) (0)(0)(0) 0 0 0 - -- 6 - -- 6  $\overline{\phantom{a}}$ 2 (%) 7 00 000 0 (0 \_ \_ **⊣**& 1 3 00 8 0 0 0 \*\*\* (16) (0) (00) (00) 4 8 00 00 00 06 06 06 00 ) 0 ô  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ \_  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ 1000 **ppm** 50 1 0 2) ( 0) ( 0 0 m 38 00 1 0 0 2 2) ( 0) ( 0) 00 (%) 0 0 0 (0 ) o ô 00 000 0 0 1 2) (2  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ 1 86 00 00  $\cup$ HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105R) 44 86 0 0 0 0 06 00 00 00 06 00 00 0 (0 0 (0  $\overline{\phantom{a}}$ \_ 250 ppm 50 m 8€ 00 00 00 00 00 0 0 0 0 0 000 00 1 (2) 1 0 ( 2) ( 0) (  $\overline{\phantom{a}}$ 2 8 。 。 。 00 00 , 2 00 1 3 **⊣** ⊗ 00 44 86 00 00 00 00 00 00 00 0 0 0 0  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ \_  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ Control 50 00 0 0 0 0 ლ §§ 00 00 00 06 00 0 (0 ) (0 ) 1 0 2) (2 (2) 2 1 ( ( 4) ( 2) ( ( ) 0 0 ) 0 0 2 8 00 0 0 2 (2  $\overline{\phantom{a}}$ 00 **€** Group Name No. of Animals on Study Grade extramedullary hematopoiesis : MOUSE BGD2F1/Cr1j[Crj:BDF1] inflammatory infiltration lymphocytic infiltration deposit of hemosiderin acidophilic cell focus basophilic cell focus clear cell focus Findings\_ : Slight scar REPORT TYPE : A1 SEX : MALE (Digestive system) STUDY NO. ANIMAL Organ liver

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PAGE:

4 8

4 - Severe		
5 · Marked	the site	
Moderate	examined at	
	animals	
1 . 511gnt	a : Number of animals examined at the site	
erade	< a >	

b : Number of animals with lesion ( c ) c : b / a \* 100 Significant difference ; \* : P  $\le$  0.05 \*\*

**★**:P≤0.01

(HPT150)

Test of Chi Square

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HISTOPATHOLOGICAL FINDINGS :NON-NEOPYASTIC LESIONS (SIMMARY)	ALL ANIMALS (0-105W)		
: 0685	: MOUSE B6D2F1/Crlj[Crj:BDF1]	3 : A1	: MALE
STUDY NO.	ANIMAL	REPORT TYPE	SEX

PAGE: 9

		Group Name No. of Animals on Study	Control 50	250 ppm	1000 pun	4000 ppm
Огван	Findings.	Grade (%) (%) (%)	3 4	1 2 3 4 (%) (%) (%) (%)	1 2 3 4 (%) (%) (%) (%)	50 1 2 3 4 (%) (%) (%) (%)
{Digestive system}	ystem)					
liver	biliary cyst	0 1 (0) (2	<50> 1 0 0 2) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 0 0
	hepatocellular hypertrophy:central	0 (0 )	(0 ) (0 ) (0	(0)(0)(0)(0)		7 0 0 0 * (14) (0) (0) (0)
(Urinary system)	(tem)					
kidney	cyst	0 0 0	<50> 0 0 0 0) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(6) (6) (6) (6) 0 0 0 0 0 0 0 0	<50> 1 0 0 ( 2) ( 0) ( 0) ( 0)
	hyaline droplet	2 0 (4) (4) (0)	(0)(0)(	(0)(0)(0)(0)(0)	(2) (0) (0) (0)	1 0 0 0 (2) (3) (4) (4)
	deposit of Hemosiderin	1 0 ( 2) ( 0)	(0)(0)(	(0) (0) (0) (0) (0) 0 0 0		33 0 0 0 **
	hyaline cast	1 0 (2) (3) (0)	(0 ) (0 ) (	(0)(0)(0)(0)(0)		(0)(0)(0)(0)
	inflammation	(0 ) (0 ) 0 0	(0 ) (0 ) (0	(0)(0)(0)(0)(0)		0 1 0 0 (0) (0) (0)
Grade < a > b ( c ) Significant	Grade 1: Slight 2: Moderate 3: Melocrate at the site beautiful b	3 : Marked 4 : Sovere site ≤ 0.01 Test of Chi Square				

BAIS4

(IIPT150)

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

: 0685 : MOUSE B6DZF1/Cr1j[Crj:BDF1]

STUDY NO. ANIMAL

REPORT TYPE : A1 SEX : MALI

PAGE: 10 4 % 4000 **ந**்நா 50 m 😪 2 % --| B 4 % 1000 ppm 50 2 3 (%) ~ <del>3</del>8 4 8 250 ppm 50 m 8€ 2 (%) - 8 44 86 Control 50 e 8 2 8 **-**|⊛ Group Name No. of Animals on Study Grade Findings

00 00 o 6 00 06 00 00 00 0 1 2 ( 0) ( 2) ( 4) ( 1 0 0 ( 2) ( 2) ( 0) ( (0)(2)(0)( 0 (0 ) (0 ) (0 ) (0) (9) (0) 2 4 00 00 0 2 5 \_  $\overline{\phantom{a}}$ 。 。 。 <u>- 3</u> 0 0 0 0 00 00 06 00 00 00 00 00 0 (0 0 0 0 0  $\overline{\phantom{a}}$ 0 2 3 0) (4) (6) (  $\overline{\phantom{a}}$ \_ 0 0 0 0  $\overline{\phantom{a}}$ 0 1 0 (0 ) 00 00 (0) (0) (0 0 2 0) ( 4) ( ) 0 0 00 2 <del>(</del>4 )  $\overline{\phantom{a}}$ 00 00 00 06 o 6 1 5 00 00 00 00 0 0 0 0 0 0 0 0 0 6 2 ( 0) ( 12) ( 4) ( \_ 00 00 00 00 000 00 000 000 ) 0 (6) ) 00 00 00 00 00 00 00 00 7 8 00 00 00 00 <u>-</u> 1 0 0 (2) (2) (3) (3) (4)  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ 0 5 2 (0) (10) (4) 1 0 0 (2) (2) (3) (4) 00 (0)(0)(0) 00 00 1 0 0 (2) (0) (0) ) 0 0 ) 0 0 00 0 0 0 0 00 lymphocytic infiltration mineralization:cortex mineralization:pelvis papillary necrosis inflammatory polyp hydronephrosis pyelonephritis scar (Urinary system) kidney Organ\_

4 : Severe 3 : Marked Grade 1: Slight 2: Moderate 3: Mc  $\langle a \rangle$  a: Number of animals examined at the site b b: Number of animals with lesion (c) c: b/a\*100 Significant difference; \*: P  $\leq$  0.05 \*\*: P  $\leq$  0.07

(IIPT150)

Test of Chi Square \*\*: P ≤ 0.01 BAIS4

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STUDY NO. : 068 ANIMAL : MOU REPORT TYPE : A1 SEX : MAL	: 0685 : MOUSE BGDZFI/Crjj[Crj:BDF1] : A1 : MALE	HISTOPATHOLOGICAL FINDINGS ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)		PAGE: 11
Organ	Findings	Group Name Control No. of Animals on Study 50 Grade   1 2 3 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 4 (%) (%) (%) (%)
{Urinary system} kidney	em) dilatation:tubular lumen	<pre></pre>	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 0 1 1 0 ( 0) ( 2) ( 2) ( 0)
	glomerulosclerosis		0 1 1 0 ( 0) ( 2) ( 2) ( 0)	0 0 1 0 (0) (0) (0) (0)	
	regeneration:proximal tubule	12 0 0 0 (24) (24) (6) (6)	14 0 0 0 0 (28) (28) (3) (4) (5)	8 0 0 0 0 (16) (16)	10 2 0 0 (20) (4) (0) (0)
ureter	dilatation	<50> 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) (0) (0)	(0)(0)(0)(0)
urin bladd	dilatation	<50> 0 4 0 0 ( 0) ( 8) ( 0) ( 0)	<50> 0 7 0 0 ( 0) ( 14) ( 0) ( 0)	(50) 0 10 0 0 ( 0) ( 20) ( 0) ( 0)	<pre></pre>
	simple hyperplasia:transitional epithelium	lium 1 0 0 0 (2) (3) (3) (3) (3)			(2) (0) (0) (0)
	xanthogranuloma	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		(0)(0)(0)(0)	0 0 0 0 0
Grade	1 . Clink 9 . Wodowata 3	9 · 16.mlol A · S.m.			

4 · Severe				Test of Chi Square	
o . warked	e site			* : P ≤ 0.01	
z - Moderate	a : Number of animals examined at the site	ith lesion			
W - 7	of animals o	b : Number of animals with lesion	100	Vil ⊶  *	
1118116 . 1	a : Number	b : Number	c:b/a*100	ignificant difference ; * * : P $\leq$ 0.05	
angla	< a >	Ъ	(°)	Significant o	

(IIPT150)

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

STUDY NO. : 0685
ANIMAL : MOUSE BGD2F1/Cr1j[Crj:BDF1]
REPORT TYPE : A1
SEX : MALE

SEX :	: MALE				PAGE: 12
Organ	Group Name No. of Animals on Study Grade	Control 504 1 2 3 4 (%) (%) (%) (%)	250 ppm 50 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 4 (%) (%) (%) (%)
(Urinary system)	em)				
urin bladd	Inyaline droplet degeneration:superficial cell of transitional epithelium	\$20\$ (0) (0) (0) (0)	(0)(0)(0)(0) 0 0 0 0 0 000	<00 ( 0) (0 ) (0 ) (0 ) (0 ) (0 ) (0 ) (	<50> 12 0 0 0 ** (24) ( 0) ( 0) ( 0)
urethra	inflammetion	<50> 0 0 0 0 ( 0) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0	<50> 0 0 0 0 ( 0) ( 0) ( 0)	(50) 0 4 0 * (0) (14) (0) (0)
(Endocrine system)	stem)				
pituitary	cyst	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 <05>	(49) 0 0 0 0 ( 0) ( 0) ( 0)	(49) 1 0 0 0 (2) (0) (0) (0)	(6) (6) (6) (6) 0 0 0 0 0 0 0 0
	lyperplasia	(0)(0)(0)(0)	0 1 0 0 (0) (0) (0)	(2) (0) (0) (0)	(0) (0) (0) (0)
	Rathke pouch	2 0 0 0 ( 4) ( 4) ( 0) ( 0) ( 0)	2 0 0 0 0 (4) (4) (6) (6)	1 0 0 0 (2) (2) (3) (4)	2 0 0 0 (4) (4) (6) (6)
paratlyroid	embryonal rest	<50> 2 0 0 0 ( 4) ( 0) ( 0) ( 0)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> 0 0 0 0 ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0

(IIPT150)

<sup>\*\*:</sup> P \le 0.01 Test of Chi Square

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

STUDY NO. : 068: ANIMAL : MOUS REPORT TYPE : A1 SEX : MAL	: 0685 : MOUSE B6DZF1/Cr1j[Crj:BDF1] : A1 : MALE	HISTOPATHOLOGICAL FINDINGS :) ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	(A	PAGE : 13
Organ	Findings	6roup Name Control No. of Animals on Study 50 Grade   1 2 3 4 (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Endocrine system) adrenal	ystem) focal fatty change:cortex	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 <05>	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 (05)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) (0 ) (0 )
{Reproductive system} testis	e system) atrophy	<50> 2 0 0 0 ( 4) ( 0) ( 0) ( 0)	(50) 2 1 1 0 (4) (2) (2) (0)	<50> 3 1 0 0 ( 6) ( 2) ( 0) ( 0)	(0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0
epididymis	mineralization inflammation	) (0 ) (0 ) 0 0 0 0 0 0 0	) (0 ) (0 ) 0 0 0 0 0 0 0 0 0 0	( 4) ( 0) ( (50) ( 2) ( 0) ( ( 2) ( 0) ( ( 2) ( 0) ( 0	0 (0 ) (0 ) 0 0 0 0 0 0 0 0 0 0 0 0 0
prostate	spermatogenic granuloma inflammation	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2 1 0 0 ( 4) ( 2) ( 0) ( 0) (50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	2 0 0 0 ( 4) ( 0) ( 0) ( 0) ( 50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	( 0) ( 0) ( 0) ( 0) ( 0) ( 1) ( 0) ( 0) ( 2) ( 14) ( 0) ( 0)

\* : P  $\leq$  0.05 \*\* : P  $\leq$  0.01 Test of Chi Square

(HPT150)

4 : Severe

3 : Marked

MARY)

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Crlj[Crj:BDF1]
REPORT TYPE : Al
SEX : MALE

PAGE: 14

	THE TAXABLE PROPERTY OF THE PR			
OrganFindings	Group Name Control No. of Animals on Study 50 trade $\frac{1}{(\%)} (\%) (\%) (\%)$	250 ppm 50 1 2 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%)
(Reproductive system)				
prep/cli gl duct ectasia		(20) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0 0	(50) 1 0 0 0 (2) (0) (0) (0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 <05>
(Nervous system)				
brain heworrhage	<00	(6) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0) (0) (0) (0) (0)
mineralization	11 0 0 0 (22) (22) (0) (0) (0)	12 1 0 0 (24) (24) (2) (0) (0)	14 0 0 0 (28) (28) (30) (30) (40)	15 0 0 0 0 (30) (30) (30) (30) (30) (30) (
spinal cord mineralization	(50) ( 2) ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0
(Special sense organs/appendage)				
eye keratitis	(50) 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 0 0 0	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 (20)
Grade 1: Slight 2: Moderate 3:) 	3 : Marked 4 : Severe : site : ≤ 0.01 Test of Chi Square			

BAIS4

(HPT150)

(IIPT150)

STUDY NO. : 068 ANIMAL : MOU REPORT TYPE : A1 SEX : MAL	: 0685 : WOUSE BGDZF1/Cr1j[Crj:BDF1] : A1 : MALE	H	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)			
				THE PARTY OF THE P		MGE	el
		Group Name No. of Animals on Study	Control 50	20 <b>1</b>	1000	4000 ppm 50	
Organ	Findings	Grade	(%) (%) (%) (%)	(%) (%) (%) (%)	1 2 3 4 (%) (%) (%) (%)	(%) (%) (%) (%)	10
(Special sens	(Special sense organs/appendage)						
eye	squamous cell metaplasia:cornea		(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0 0	<50> <50> (50) (50) (50) (50) (50) (50) (50) (50)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	
Harder gl	degeneration		<49> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	(50) 0 0 0 0 ( 0) ( 0) ( 0)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	
	lymphocytic infiltration		2 0 0 0 ( 4) ( 4) ( 0) ( 0) ( 0)	1 0 0 0 ( ) ( ) ( ) ( )	1 0 0 0 (2) (2) (3) (4)	2 0 0 0 (4) (4) (6) (6) (6)	
(Musculoskeletal system)	stal system)						
muscle	mineralization		( 0) ( 0) ( 0) ( 0) ( 0)	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 <05)	
	inflammatory infiltration				(0)(0)(0)(0)(0)	1 0 0 0 ( ) ( ) ( ) ( )	
(Body cavities)	35)						
retroperit	inflammatory infiltration		(0) (0) (0) (0) (0) (0)	<pre></pre>	<00	(0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	
Grade 1 : Slight  (a) a : Number  b b : Number  (c) c : b / a *  Significant difference :	1: Slight 2: Moderate 3::) a : Muchor of animals examined at the site b: Number of animals with lesion c: b / a * 100 difference; $*: P \leq 0.05$ **: $P \leq 0.05$	Marked 01 Test of	4 : Severe Chi Square				

#### TABLE L 4

HISTOPATHOLOGICAL FINDINGS:

NON-NEOPLASTIC LESIONS:

FEMALE: ALL ANIMALS

BAIS4

(IIPT150)

Priority   Priority	STUDY NO. ANIMAL REPORT TYPE SEX	: 0685 : MOUSE BGD2F1/Cr1j[Crj:BDF1] : A1 : FEMALE	ALL	HISTOPATHOLOGICAL FINDINGS ALL ANIMALS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)	۵	PAGE	91 : 19
Seed   Color   Color	Organ	Findings	Group Name No. of Animals on Stu Grade	Control 50 1 2 3 %) (%) (%)	250 ppm 50 3 (%) (%)	1000 µpm 50 2 3 (%) (%)	(%)	_la
State   Care	{Integumenta	nry system/appandage)						
Secondarie	skin/app	scat		<50> 1 0 0 2) ( 0) ( 0) (	(20) (0 ) (0 ) (0 ) (0 ) (0 ) (0 ) (0 )	(50>) (0 (0) (0 (0) (0) (0) (0) (0) (0) (0)	2 4) ( 0	0.3
evesinophilic change:effactory epithelium  (10) (0) (0) (0) (0) (0) (0) (0) (0) (0) (	(Respiratory	/ system]						
lic change-olfactory epithelium (10) ( 0) ( 0) ( 0) ( 6) ( 2) ( 0) ( 0) ( 6) ( 6) ( 6) ( 6) ( 6) ( 6	nasal cavit			(50) (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	<50> 0 0 0 0) ( 0) ( 0) (	(50) 1 0 0 2) ( 0) ( 0) (	0 ) (0	c =
lic change: respiratory epithelium  (50) (10) (0) (0) (60) (60) (60) (60) (60) (60)		eosinophilic change:olfactory epithe		0 (0 )	3 1 0 6) (2) (0) (	4 0 0 8 ( 0) ( 0) (	6 0 12) ( 0)	c =
ion: foreign body  ( 0) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0) ( 0		eosinophilic change:respiratory epit		25 5 0 50) (10) (0) (	30 3 0	26 6 0 52) (12) (0) (	30 6 0 60) (12) ( 0) (	0 (0
ry metaplasia:olfactory epithelium ( 2) ( 0) ( 0) ( 0) ( 0) ( 4) ( 0) ( 0) ( 0		inflammation:foreign body	Š	0 0 0 0	0 1 0 0 0) ( 2) ( 0) (	0 0 0 0	1 0 2) ( 0)	. =
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		respiratory metaplasia:olfactory epi		1 0 0 0 2) ( 0) (	2 0 0 4) ( 0) (	0 0 0 0	1 0 2) ( 0)	0.3
2 : Moderate 3 : Marked of animals examined at the site of animals with lesion 100   ∗ : P ≤ 0.05   ∗ : P ≤ 0.05   ∗ : P ≤ 0.01		respiratory metaplasia:gland		0 (0 )	0 (0 ) (0 )	0 (0 )	2 0 0 4) ( 0) ( 0) (	0 (0
	Grade < a > b b ( c ) Significant	2 : Modoratc of animals examined at the of animals with lesion : 100 * : P ≤ 0.05 ** : P	farked 01	Sovero				

4000 µрт 50 e 8€ 2 8 - 88 4 % 2 3 (%) 1000 **ppm** 50 - 88 HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105#) 4 % 250 µµm 50 2 3 (%) (%) **-**|⊛ 2 3 4 (%) (%) (%) Control 50 - 38 Group Name No. of Animals on Study Grade STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Cr1j[Crj:EDF1]
REPORT TYPE : A1
SEX : FEMALE Findings\_ {Respiratory system} nasal cavit Organ

PAGE: 17

4 %

squamous cell metaplasia:respiratory epithelium	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<pre></pre>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 2 0 0 ( 4) ( 0) ( 0) ( 0)
ulcer:respiratory epithelium		1 0 0 0 0 (2) (2) (3) (4)	(0) (0) (0) (0)	
alrophy:olfactory epithelium	(0)(0)(0)(0)		0 1 0 0 (0) (0) (0)	
eosinophilic change	<50> 2 2 0 0 ( 4) ( 4) ( 0) ( 0)	<50> 2 1 0 0 ( 4) ( 2) ( 0) ( 0)	<50> 2 0 0 0 ( 4) ( 0) ( 0) ( 0)	<50> 4 3 0 0 (8) (6) (0) (0)
congostion	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0	<pre></pre>	<50> 0 1 0 ( 0) ( 2) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 (20)
inflammatory infiltration		(0)(0)(0)(0)(0)		1 0 0 0 (2) (3) (4) (4)
lymphocytic infiltration	(0) (0) (0) (0)	1 0 0 0 ( 2) ( 2) ( 0) ( 0) ( 0)	1 0 0 0 0 0 0 (2) (2) (3) (4) (6)	(0)(0)(0)(0)

b b: Number of animals with losion ( c ) c: b / a \* 100 Significant difference; \*: P  $\leq$  0.05 \*\*

\*\*: P ≤ 0.01 Test of Chi Square

(IIPT150)

nasopharynx

lung

(IIPT150)

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

PAGE: 18

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Cx1j[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE

		Group Name No. of Animals on Study	Control 50	250 ppm 50	1000 µpm 50	прп	4.	4000 ppm 50	
Organ	Findings	-100	(%) (%) (%)	1 2 3 4 (%) (%) (%)	(%) (%) (	(%) (%)	(%) (%)	(%) (%)	8 8
(Respiratory system)	system)								
lung	accumulation of foamy cells	0 0 0	<50> (0) (0) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<050> 0 0 ( 0) ( 0) (	(O ) (O	0 1 (0) (2)	<50> 1 0 2) ( 0) (	0 0
	bronchiolar-alveolar cell hyperplasia	0 0	(0 ) (0 ) (0	(2) (0) (0) (0)	0 0	(0 ) (0	1 0 (2) (0)	0 (0 )	0 0
	accumulation:macrophage	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
	degeneration:blood vessel	0 ) (0 )	(0 ) (0 ) (0	(0)(0)(0)(0)	1 0 (2) (0) (	(0 ) (0	2 4 ( 4) ( 8)	0 (0 )	* (î
{Hematopoietic system}	ic system)								
ьоне ваттом	granulation	2 0 ( 4) ( 0	<50> 0 0 0 0) ( 0) ( 0)	<pre></pre>	<05> (0 ) (0 ) (0 )	0 0	(O) (O)	<50> 0 0 0) ( 0) (	0 (0
	increased hematopoiesis	17 C	(0 ) (0 ) (0	11 0 0 0 0 (22) (22) (3) (3) (3)	18 0 (36)	(O ) (O	36 0 (72) (0)	0 (0 )	* 0 0
	granulopoiesis:increased	0 (0 )	(0) (0) (0		1 0 (2) (0) (	(0 ) (0	(0) (0)	0 (0 )	0 0
Grade < a > b b ( c )	1 : Slight 2 : Modorate 3 : Malor of animals examined at the site b : Number of animals with lesion c : b / a * 100	3: Markod 4: Sovore site							

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

(HPT150)

FINDINGS : NON-NEOPLASTIC LESIONS (SUMMARY)	SW)	
HISTOPATHOLOGICAL	ALE ANTMALS (0-105W)	

STUDY NO. : 068 ANIMAL : MOU REPORT TYPE : A1 SEX : FEM	: 0685 : MOUSE BEDZF1/Cr1j[Crj:BDF1] : A1 : FEMALE	HISTOPATHOLOGICAL FINDINGS :N ALL ANIMALS (0-105%)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105%)		PAGE: 19
Organ	Findings	Group Name No. of Animals on Study Grade (%) (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%) (%)
{Hematopoietic system} lymph node lympha	ic system) lymphadenitis	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)
spleen	atrophy	(50) 0 1 0 0 (0)(2)(0)(0)	<00 ( 0) ( 0) ( 0 ) ( 0 ) ( 0 ) ( 0 ) ( 0 )	(6 ) (0 ) (0 ) (0 ) 0 0 0 0 (0 )	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)
	deposit of hemosiderin	19 0 0 0 (38) (38) (0) (0) (0)	10 20 0 0 ** (20) (40) (0) (0)	9 26 0 0 ** (18) (52) (0) (0)	14 29 1 0 *** ( 28) ( 58) ( 2) ( 0)
	osseous metaplasia				1 3 0 0 (2) (3) (6) (0) (0)
	extramedullary hematopoiesis	11 10 0 0 (22) (20) (0) (0)	15 6 1 0 (30) (12) (2) (0)	16 16 0 0 (32) (32) (0) (0)	28 10 0 0 *** (56) (20) (0) (0)
	engorgement of erythrocyte				12 1 0 0 ** ( 24) ( 2) ( 0) ( 0)
	follicular hyperplasia		2 0 1 0 (4) (0) (2) (0)	1 0 0 0 (2) (2) (3) (4)	(0)(0)(0)(0)
{Circulatory system} heart	system) Lhrombus	2 0 0 0 (4) (6) (6) (6)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	<56> 0 0 0 0 0 0 0 0 0 0 0 0

**★**: P ≤ 0.01

\* :  $P \le 0.05$ 

Significant difference;

(HPT150)

PAGE: 0 (0 0 0 0 0 0 0 0 0 2 3 (%) 4000 **որ**ու 50 (0)(0)(0) 2 0 0 ( 4) ( 0) ( 0) (0 ) (0 ) (0 ) (0 ) 0 0 7 % 1 0 0 0 ( 2) ( 2) ( 0) ( 0) ( 0) 00 00 00 00 00 4 8 000 0 (0  $\smile$ \_ 88 1000 ppm 50 1 0 0 2) ( 0) ( 00 (0)(0)(2) 0 ) (0 ) (0 ) 0 (0 (0 ) 1 0 (2) ( 0) ( 2 (%) **⊣** §€ HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) 0 0 0 0 (0 ) (0 ) (0 (0 ) (0 ) (0 0 o ô 0 (0 ) (0 ) (0 (0)(0)(0)(0)(0) 4 % 0 0 0 250 ppm 50 8 2 (%) 3 (9 ) 000 000 0 0 1 (2) - <del>3</del>8 4 8 00 06 00 00 00 00 3 0 0 ( 1 0 0 ( ) ( ) ( 1 0 0 ( 2) ( 0) ( 0) ( 0 0 0 0 1 0 0 ( 2) ( 2) ( 0) ( 0 0 0 0 Control 50 ლ წ 2 (%) 4 : Severe · 89 Group Name No. of Animals on Study Grade 3 : Marked 1: Slight 2: Moderate 3: Me a : Number of animals examined at the site b : Number of animals with losion c : b / a \* 100 STUDY NO. : 0685
ANLMAL : MOUSE BGDZFL/Crij[Crj:BDF1]
RGPORT TYPE : A1
SEX : FEMALE myocardial fibrosis mineralization degeneration arteritis dysplasia arteritis Findings. (Circulatory system) (Digestive system) Grade < a > b ( c ) tongue heart Organ

20

4 %

00

06

00

00

00

00

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

(IIPT150)

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

STUDY NO. : 0685
ANIMAL : MOUSE B6DZF1/Crlj[Crj:BDF1]
RDFORT TYPE : A1
SEX : FEMALE

SEX :	: FEMALE				PAGE : 21
Огван	Findings	Group Name  No. of Animals on Study  Grade  (%) (%) (%) (%)	250 ppm 50 1 2 3 4 (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%) (%)
(Digestive system) salivary gl	stem) Xanthogranuloma	(0) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0)	(0) (0) (0) (0) 0 0 0 0 <05>	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)
stomach	hyperplasia:forestomach	<50> 2 0 0 0 ( 4) ( 0) ( 0) ( 0)	(0)(0)(0)(0)	<200> (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)
	erosion:glandular stomach		1 0 0 0 (2) (2) (3) (4)	(0)(0)(0)(0)(0)	0 0 0 0 0 0
	hyperplasia:glandular stomach	5 0 0 0 (10) (10) (10) (10) (10)	6 0 0 0 ( 12) ( 0) ( 0) ( 0)	8 0 0 0 0 (16) (16)	4 0 0 0 0 ( 8) ( 8) ( 0) ( 0)
liver	congestion	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	<50> 0 1 0 0 ( 0) (2) ( 0) ( 0)	<50> (0) (0) (0) (0) (0)	(0) (0) (0) (0) (0)
	angiectasis	0 2 0 0 (0) (4) (0) (0)	0 2 0 0 (0) (4) (0) (0)	0 0 (0) (0) (0)	0 4 0 0 (0) (0)
	necrosis:central			(0)(0)(0)(0)	1 0 0 0 ( 2) ( 3) ( 3)
***************************************	***************************************				

(IIPT150)

BAIS4

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

PAGE: 22

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE

Organ	oroup No. of Grade Grade	Group Name Control No. of Animals on Study 50 Grade (%) (%) (%) (%)	250 ppm 50 (%) (%) (%) (%)	1000 ppm 50 1 2 3 4 (%) (%) (%)	4000 ppm 50 4000 (%) (%) (%) (%) (%) (%) (%)	اءاء
(Digestive system)	system)					
liver	necrosis:focal	(50) 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> <50> (0) (2) (0) (0)	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	<50> (0) (0) (0) (0) (0) (0) (0) (0) (0) (0)	0 6
	fatty change:central		0 0 0 0 0	(0)(2)(0)(0)	0 ) (0 ) (0 ) (0 )	0 (0
	deposit of hemosiderin			2 0 0 0 0 (4) (4) (6) (6)	34 0 0 0 ( 0) ( 0) ( 0	<b>*</b> (0
	lymphocytic infiltration	1 0 0 0 (2) (2) (3) (4) (4)		2 0 0 0 0 (4) (4) (6) (6)	1 0 0 0 ( ) ( ) ( ) ( )	0 0
	granulation	2 1 0 0 (4) (2) (0) (0)		2 0 0 0 (4) (4) (6) (6)	0 ) (0 ) (0 ) (0 )	o 6
	clear cell focus		0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0			o 6
	acidophilic cell focus	1 0 0 0 (2) (2) (3) (4) (5)		(0)(2)(0)(0)	1 0 0 0 (2) (3) (4 0) (4 0)	06
	hepatocellular hypertrophy:central	(0) (0) (0) (0) (0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0	0 0 0 0 0	7 0 0 0 (14) (14) (15) (15) (15)	* (0
Grade < a > b	1: Slight 2: Moderate 3: Ms a : Number of animals examined at the site b: Number of animals with lesion	3 : Marked 4 : Severe site				

	03:1]		
: 0685	MOUSE BGD2F1/Cr1j[Crj:BDF1]	A1	FEMALE
	-		
STUDY NO.	ANIMAL	REPORT TYPE : A1	SEX

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

PAGE: 23

1000 ppm 50 50 2 3 4 1 2 3 4 (%) (%) (%) (%) (%) (%)	(50) (0) (0) (0) (0) (0) (0) (0) (0) (0) (	(50)       (50)         2       0	0) (0) (0) (34) (0) (0) (0)	0) (0) (0) (0) (5) (0) (0)	0) (0) (0) (2) (0) (0) (0)	0) (0) (0) (0) (12) (0) (0)	2) (0) (0) (0) (0) (0) (0)	
-  %	0 0	10 2 ( 20) ( 4	0 (0 )	0 0	1 (2) (-2)	0 0	0 0 0	
250 ppm 50 1 2 3 4 (%) (%) (%) (%)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 0 0 0 0	<pre>&lt;50&gt; 6 0 0 (12) (0) (0) (0)</pre>	1 0 0 0 (2) (2) (3) (4)	0 0 0 0 0	3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0)	(0)(0)(0)(0)(0)	
Animals on Study 50 4 (%) (%) (%) (%) (%) (%)	(50) 0 0 1 0 ( 0) ( 0) ( 2) ( 0)	<50> 7 0 0 (14) (0) (0) (0)	(0) (0) (0) (0)	(0)(0)(0)(0)	(0)(0)(0)(0)	0 1 0 0 (0) (0) (0) (0)		4 : Sovere
Group Name No. of Animal. Grade	system) atroply	stem) hyaline droplet	deposit of hemosiderin	inflammation	lymphocytic infiltration	scar	inflammatory polyp	Grade 1: Slight 2: Moderate 3: Marked <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 ≤ 0.01 Test</a>
Огван	(Digestive system) pancreas at	(Urinary system) kidncy						Grade < a > b ( c ) Significant

BAIS4

(IIPT150)

HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W) : 0685 : MOUSE BGDZF1/Cr1j[Crj:BDF1]

REPORT TYPE : A1 SEX : FEMALE

STUDY NO.

PAGE: 24

**\*** 0 0 4 8 00 00 00 00 00 00 (0)(2)(0)( (2)(2)(0)( 1 1 0 (2) (2) (0) ( 0 0 0 0 2 3 (%) (%) 4000 ppm 50 0 0 0 1 0 0 ( 2) ( 0) ( 0) o ô ` 2 0 0 ( 4) ( 0) ( 0) 3 (9) 4 (8) 14 (28) **-**|€ 00 4 % 00 00 00 00 00 00 00 0 2 1 0) (4) (2) ( \_  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ \_  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ 1000 ppm 50 2 3 (%) (%) 0 0 0 0 0 0 0 0 00 00 00 0 1 0 ( 0) ( 2) ( 0) 00 0 6 0 0 000 0 0 2 (4) (6) 000 00 - -- 6  $\overline{\phantom{a}}$  $\overline{\phantom{a}}$ 1 (2 00 **⊣** 8€ 0 1 0 0 (0) (0) (0) (0) 00 00 44 86 00 00 00 00 00 . 6 ි ට - -- 6 - -0 0 0 0 0 0 \_ ቪ 00 00 e 8€ 0 0 0 0 (0 (0 0 0 0 2) (0) (0 1 0 (2 000 250 2 (%) 00 **-** 8 0 0 00 0 0 o 6 . 4 86 0 2 0 ( 0) ( 4) ( 0) ( 0) 00 00 00  $\overline{\phantom{a}}$ 2 3 (%) (%) \_ Control 50 0 0 0 0 0 0 0 0 (6) 0 0 (0) (0) (0) (0) 00  $\overline{\phantom{a}}$ 00 000 000 000 (2) 000 - 8 Group Name No. of Animals on Study Grade hyaline droplet degeneration:superficial cell of transitional epithelium regeneration:proximal tubule dilatation:tubular lumen mineralization:papilla desquamation:pelvis papillary necrosis hydronephrosis dilatation Findings. (Urinary system) urin bladd kidney Organ

BAIS4

Test of Chi Square

**★**: P ≤ 0.01

(HPT150)

Grade 1 : Slight 2 : Moderate 3 : Ma  $\langle$  a  $\rangle$  a : Number of animals examined at the site b b : Number of animals with lesion ( c ) c : b / a \* 100 Significant difference ; \* : P  $\leq$  0.05 \*\* : P  $\leq$  0.0

4 : Severe

3 : Marked

(HPT150)

Y NO. IAL ORT TYPE	: 0685 : MOUSE BGDZF1/Cr1j[Crj:BDF1] : A1	HISTOPATHO ALL ANIMAI	DLOGICAL FINDINGS :N. JS (0-105W)	HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANIMALS (0-105W)			
SEX	: FEMALE					PAGE	
		Group Name No. of Animals on Study	Control 50	250 ppm 50	1000 ppm 50	1000 50	
Organ	Findings	(%)	(%) (%) (%)	(%) (%) (%)	(%) (%) (%) (%)	(%) (%) (%) (%)	Ja
(Endocrine system)	ystem)						
pituitary	angiectasis	0	(50)	<20> 0	<50> 0	<49> 0 0	
		) (0 )	(0 ) (0 ) (0	(0 ) (0 ) (0 ) (0 )	(4) (0) (0) (0)	(0) (0) (0) (0)	_
	hyperplasia	) (01)	3 0 0 (9) (9)	(10) (0) (0) (0)	0 0 0 (91)	3 1 0 0 (6) (7) (7) (7) (8) (7)	$\widehat{}$
	Rathke pouch	3 (9 )	(0) (0) (0				
adrena]	cyst	0 0	<50> 1 0 0 2) ( 0) ( 0)	<00	<pre></pre>	(0) (0) (0) (0) (0) (0)	
	spindle-cell hyperplasia	12 ( 24) (	(0) (0) (0	10 0 0 0 0 (20) (20) (0) (0)	(0)(0)(0)(91)	0 0 0 6	
	focal fatty change:cortex	1 ( 2) (	(0) (0) (0		(0) (0) (0) (0)	1 0 0 0 (2) (2) (3) (4)	
	fatty change:corticomedullary junction	0 0 0	(0 ) (0 ) (0	0 1 0 0 (0) (0) (0) (0)	(0)(0)(0)(0)		
{Reproductive system}	e system)						
ovary	thrombus	0 (0 )	<50> 0 0 0 0) ( 0) ( 0)	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)	<50> 0 0 0 0 ( 0) ( 0) ( 0) ( 0)	
Grade < a > b b ( c ) Significant	Grade I : Slight 2 : Moderate 3 : N < a > a : Number of animals examined at the site b : Number of animals with lesion ( c ) c : b / a * 100 Significant difference : * : P $\leq$ 0.05 ** : P $\leq$ 0.	3: Marked 4: Severe site ≤ 0.01 Test of Chi Square					

PAGE: 25

\*\* : P ≤ 0.01

\* :  $P \le 0.05$ 

(HPT150)

PAGE: 26 ( 0) ( 6) ( 0) ( 0) (0)(0)(0)(0)(0) 4 0 0 0 ( 8) ( 8) ( 9) ( 9) 2 3 (%) (%) 0 0 0 0 (14) (2) (0) ( 0 0 0 0 4000 ppm 50 **⊣** § 00 4 % 7 0 0 0 (14) (0) (0) (0) 00 06 00 00 0 (0 ) (0 ) (0 ) 12 0 0 (24) (24) (0) (0) (0) 0 0 0 0 0 0 0 0 0 0 0 0 1000 ppm 50 2 3 (%) (%) 7 86 HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY)
ALL ANIMALS (0-105W) 4 8 3 0 0 0 0 ( 0) ( 0) 0 1 0 0 (0) (0) (0) 00 00 10 0 0 0 0 (20) (20) (30) (30) (0)(0)(0)(0)(0 - -- 6 0 0 e 8 nh 0 (0 ) (0 ) 0 0 0 2) (2 250 <sub>1</sub> 20 88 0 0 **⊣** §€ 4 86 3 0 0 0 0 (0) (0) (0 ) (0 ) (0 ) (0 ) 00 00 00 00 10 0 0 0 (20) (20) (20) 1 0 0 ( 2) ( 2) ( 0) ( 0 0 0 0 1 0 0 (2) (2) (3) (3) Control 50 2 3 (%) 4 : Severe 8 Group Name No. of Animals on Study Grade 1 3 : Marked 1: Slight 2: Moderate 3: Mas a: Number of animals examined at the site b: Number of animals with losion c: b/a\*100 cystic endometrial hyperplasia : MOUSE B6D2F1/Cr1j[Crj:BDF1] inflammatory infiltration hyperplasia:gland dilatation hemorrhage Findings. REPORT TYPE : A1 SEX : FEMALE (Reproductive system) cyst STUDY NO. : 0685 ANIMAL : MOUSE (Nervous system) uterus Organ brain ovary

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LES I ONS
: NON-NEOPLASTIC
FINDINGS

(SUMMARY)

HISTOPATHOLOGICAL FIN ALL ANIMALS (0-105W)

STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Cr1j[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE

SEX : 1	: PEMALE					PAGE: 27
Organ	Findings.	Group Name No. of Animals on Study Grade (%)	Control 50 4 (%) (%)	250 ppm 50 1 2. 3 4 (%) (%) (%) (%)	1000 ppm 50 4 (%) (%) (%) (%)	4000 ppm 50 1 2 3 4 (%) (%) (%)
{Nervous system}	(a					
brain	mineralization	10 ( 20) (	<50> 0 0 0 0) ( 0) ( 0)	<50> 6 0 0 ( 12) ( 0) ( 0) ( 0)	<50> 9 0 0 0 (18) ( 0) ( 0) ( 0)	<50> 14 0 0 0 ( 28) ( 0) ( 0) ( 0)
(Special sense	(Special sense organs/appendage)					
cyc	keratilis	0	<50> 0 0 0 0) ( 0) ( 0)	<pre></pre>	(0) (0) (0) (0) 0 0 0 0 0 0 0 0	$   \begin{array}{ccccccccccccccccccccccccccccccccccc$
Harder gl	lymphocytic infiltration	0 0	\$20\$ 0 0 0 0 0 0 0 0 0	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	<50> 1 0 0 0 ( 2) ( 0) ( 0) ( 0)	(0) (0) (0) (0)
{Musculoskeletal system}	al system)					
muscle	mineralization	0 0	<50> 1 0 0 2) ( 0) ( 0)	(50) (2) (0) (0)	<50> 2 0 0 ( 0) ( 0) ( 0)	(0) (0) (0) (0) 0 0 0 0 (0) (0) (0)
hone	deformity	0 0	(20) (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	(0)(0)(0)(0) 0 0 0 0 0 0 0 0 0 0 0	<50> 0 1 0 0 ( 0) ( 2) ( 0) ( 0)	(0 ) (0 ) (0 ) (0 ) 0 0 0 0 0 <05>

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

++: P ≤ 0.01 Test of Chi Square

BAIS4

(IIPT150)

PAGE: 28 0 0 0 0 0 (0)(0)(0)(0) 4000 ppm 50 2 3 (%) (%) **<20** - <del>8</del> 4 8 (0 ) (0 ) (0 ) (0 ) 00 0 0 0 0 1000 **ppm** 50 2 3 (%) (%) 7 86 HISTOPATHOLOGICAL FINDINGS :NON-NEOPLASTIC LESIONS (SUMMARY) ALL ANLMALS (0-105%) 4 8 2 0 0 0 ( 4) ( 0) ( 0) ( 0) ( 2) ( 0) ( 0) 2 3 (%) (%) 25**0 ppm** 50 - 80 4 % (0) (0) (0) (0) 0 0 0 0 0 2 3 (%) (%) Control 50 Group Name No. of Animals on Study Grade I STUDY NO. : 0685
ANIMAL : MOUSE BGDZF1/Crlj[Crj:BDF1]
REPORT TYPE : A1
SEX : FEMALE osteosclerosis inflammation Findings\_ {Musculoskeletal system} (Rody cavities) peri toneum Organ bone

4 %

	1 : Slight 2 : Moderate	3 : Marked	4 : Severe
(a) a: Number	a : Number of animals examined at the site	t the site	
b b : Number	b : Number of animals with lesion	_	
(c) c:b/a*100	. 100		
ignificant difference ; * : P ≤ 0.05		**: P ≤ 0.01 Tes	Test of Chi Square
HPT [50)			

#### TABLE O 1

## NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: MALE

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Grate Name   Gra				***************************************	THE PROPERTY OF THE PROPERTY O	
SITE   Liung   10,00   4/56 ( 8.0)   7/50 ( 14.0)   7/50 ( 14.0)   7/50 ( 14.0)   7/50 ( 14.0)   7/50 ( 10.0)   7/50 ( 14.0)   7/50 ( 10.0)	Group Name	Control	250 ppm	1000 при	4000 ppm	
S/50 (10.0)		SITE : lung TUMOR : bronchiolar—alveola	ir adenoma			
11.43	Tumor rate					
11.33	Overall rates(a)	5/50(10.0)	4/50(8.0)	7/50(14.0)	4/50(8.0)	
P = 0.4743   P = 0.4743	Adjusted rates(b)	11. 43	10.34	19.35	10.00	
D = 0.4743   SITE : lung   D = 0.5500   D = 0.3786   P = 0.3786   D = 0.5500   D = 0.3786   P = 0.3886   P = 0.4786   P	Ferminal rates(c) atistical analysis	3/31(9.7)	3/29(10.3)	5/29( 17.2)	1/16( 6.3)	
P = 0.4743   SITE : lung   F = 0.5000   P = 0.3788   P = 0.500   P = 0.3788   P = 0.570 ( 10.0)   8/50 ( 16.0)   19.35	Peto test					
st(e) P = 0.7356  p = st(e) P = 0.7356  p = 0.5000  SITE : lung  TUMOR : bronchiolar-alveolar carcinoma  5/50(10.0)  P = 0.5588  4/31(12.9)  P = 0.5588  10.50  P = 0.5588  P = 0.5000  P = 0.2768  P = 0.5000  P = 0.2768  P = 0.2	Standard method(d)	= d				
P = 0.3788   P = 0.3788   P = 0.5000   P = 0.3788   P = 0.5000	Prevalence method(d)	P = 0.4743				
SITE   Lung   TUMOR   bronchiolar-alveolar carcinoma   5/50(16.0)   8/50(16.0)   18.35   19.	Compined analysis(d) Cochran—Armita <i>me</i> test(e)	P = 0 7395				
SITE : lung   TUMOR : bronchiolar-alveolar carcinoma   5/50(10.0)   6/50(12.0)   8/50(10.0)   13.89   13.89   14/29(13.8)   15.35   14/31(12.9)   4/29(13.8)   5/29(17.2)   19.35   19.35   11/20   19.35	Fisher Exact test(e)			11	P = 0, 5000	
5/50(10.0)   6/50(12.0)   8/50(16.0)     13.89			r carcinoma			
5/50(10,0)   6/50(12,0)   8/50(16,0)     13.89	mor rate					
13.89	verall rates(a)	5/50(10.0)	6/50(12.0)	8/50(16.0)	1/50(-2.0)	
H 4/31 ( 12. 9) 4/29 ( 13. 8) 5/29 ( 17. 2)  P = 0.5588  Str = 0.0595  P = 0.500  P = 0.500  P = 0.2768  P = 0.2768  P = 0.2768  P = 0.500  P = 0.2768  P = 0.2768  P = 0.500  P = 0.2768  P = 0.500  P = 0.2768  P = 0.2768  P = 0.500  P = 0.2768  P	djusted rates(b)	13.89	16.67	19.35	6, 25	
P = 0.5588	erminal rates $(c)$	4/31(12.9)	4/29 (13.8)	5/29(17.2)	1/16(6.3)	
P = 0.5588   P = 0.8969     St(c)	atistical analysis					
	010 Lest	0000				
st(c)	Dente   method (d)	F = 0. 5565				
SITE : lung  SITE : lung  TUMOR : bronchiolar-alveolar carcinoma  10/50(20.0)  10/50(20.0)  26.67  7/31(22.6)  P = 0.2768  P = 0.500  14/50(28.0)  26.67  26.67  27.39 (24.1)  P = 0.5588  P = 0.588  P = 0.8835  P = 0.8835  P = 0.8835  P = 0.5984  P = 0.5984	Frevarence method(d) Combined analysis(d)	7 = 0.0/3/ D = 0.8969				
SITE : lung  SITE : lung  TUMOR : bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma $10/50(20.0)$ $25.00$ $10/50(20.0)$ $14/50(28.0)$ $25.67$ $35.48$ $7/31(22.6)$ $10/29(24.1)$ $10/29(34.5)$	Compiled analysis(d)	F = 0.0909				
SITE : lung  TUMOR : bronchiolar—alveolar carcinoma  10/50(20.0)	ochran armitage test(e) Isher Exact test(e)	r = 0.00%	P = 0.5000	P = 0. 2768	P = 0.1022	
SITE : lung  TUMOR : bronchiolar—alveolar adenoma, bronchiolar—alveolar carcinoma  10/50 ( 20. 0)						
10/50( $20.0$ ) 10/50( $20.0$ ) 10/50( $20.0$ ) 14/50( $28.0$ ) 35.48 7/31( $22.6$ ) 7/31( $22.6$ ) 7/29( $24.1$ ) 10/29( $24.1$ ) 10/29( $34.5$ ) 10/29( $34.5$ ) 11/29( $24.1$ ) 10/29( $24.1$			r adenoma hronchiolar—alveolar carcinoma			
10/50( $20.0$ ) $10/50( 20.0)$ $14/50( 28.0)$ $25.00$ $26.67$ $35.48$ $7/31( 22.6)$ $7/31( 22.6)$ $7/29( 24.1)$ $10/29( 34.5)$	mor rate					
25.00 26.67 35.48 7/31(22.6) 7/29(24.1) 10/29(34.5) 10/29(34.5) 26.67 35.48 26.67 36.48 27/31(22.6) 7/29(24.1) 10/29(34.5) 27/31(22.6) 7/29(24.1) 10/29(34.5) 27/31(22.6) 7/29(24.1) 10/29(34.5) 28/305 7/31(22.6) 7/29(24.1) 10/29(34.5) 29/305 7/29(24.1) 10/29(34.5)	Overall rates(a)	10/50(20.0)	10/50 ( 20.0)	14/50(28.0)	5/50(10.0)	
7/31 (22.6) 7/29 (24.1) $10/29$ (34.5) $7/29$ (24.1) $10/29$ (34.5) $9 = 0.5588$ $9 = 0.8084$ $9 = 0.1002$ $9 = 0.1002$ $9 = 0.5984$ $9 = 0.2415$ $9 = 0.2415$	Adjusted rates(b)	25.00	26.67	35.48	12.50	
<ul> <li>p ± 0, 5588</li> <li>f) p = 0, 8084</li> <li>f) p = 0, 8084</li> <li>f) p = 0, 1002</li> <li>f) p = 0, 5984</li> <li>f) p = 0, 2415</li> <li>f) p = 0, 5415</li> </ul>	ferminal rates(c)	7/31(22.6)	7/29 (24.1)	10/29(34.5)	2/16(12.5)	
method (d) $p = 0.5588$ = method (d) $p = 0.8084analysis (d) p = 0.8305analysis (e) p = 0.1002= 0.5984= 0.5984= 0.5984$	atistical analysis					
V = 0.3585 $P = 0.8084$ $P = 0.8305$ $P = 0.1002$ $P = 0.5984$ $P = 0.2415$	eto test	6				
F = 0.0004 $P = 0.8305$ $P = 0.1002$ $P = 0.5984$ $P = 0.2415$	Standard method(d)	P = 0,5588				
F = 0.3595 P = 0.1002 P = 0.5984 P = 0.2415	Frevalence method(d)	F = 0.8084				
P = 0.5984 $P = 0.2415$	Combined analysis(d)	F = 0.8303				
	Fisher Exact test(e)	1 0:1006	P = 0 5984	D = 0 9415	D = 0 1213	

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SITE TUMOR 6/8 5/8 5 sis (d) P = ( od(d) P = ( is(d) P = ( test(e) P = ( st(e) P = ( test(e) TUMOR	6/50(12.0) 9.68 3/31(9.7) = 0.5931 = 0.6406 = 0.6976 = 0.1956 : spleen	4/50 ( 8.0) 10.34 3/29 ( 10.3)			
6/7 6/7 3/7 3/7 3/7 1) P = ( 1) P = ( 1) P = ( 2) P = ( 2) P = ( 3/7 1) P = ( 3/7 1) P = ( 4/7) P = ( 4/7) P = ( 4/7) P = ( 4/7) P = ( 5/7) P =	( 12. 0) 9. 68 ( 9. 7) 5931 6406 1956 spleen hamonolione	4/50 ( 8.0) 10.34 3/29 ( 10.3) P = 0.3703			
6/50( 3/31( 3/31( 3/31(  P = 0.56  P = 0.66  Str(e) P = 0.16  SITE : TUMOR :		4/50 (8.0) 10.34 3/29 (10.3) P = 0.3703			
3/31( P = 0.56  P = 0.66  St (e) P = 0.16  St (e) P = 0.11  SITE  TUMOR  TUMOR		3/29 (10.3) $P = 0.3703$	3/50( 6.0)	2/50( 4.0)	
P = 0.55  P = 0.65  P = 0.65  St (e) P = 0.15  SITE :  TUMOR :		II	10.34 3/29(10.3)	6.25 1/16( 6.3)	
malysis (d) P = 0.66 itage test(e) P = 0.15 ct test(e) SITE : TUMOR :		II.			
ct test(e) SITE : TUMOR :		0			
SITE : TUMOR :			P = 0.2435	P = 0.1343	
<u> </u>					
	,				
Overall rates(a) 1/50(	1/50( 2.0)	0/50( 0.0)	6/50(12.0)	2/50( 4.0)	
	( 3.2)	0/29( 0.0)	3/29(10.3)	0.23	
Statistical analysis					
method(d)	***				
Prevalence method(d) P = 0.2366	2366				
	C C C C				
Cochran-Armitage test(c) P = 0.65 Fisher Exact test(c)	6866	P = 0.5000	P = 0.0559	P = 0.5000	
SITE : TUNOR :	spleen hemangiosarcoma				
Tumor rate Overall rates(a) 0/50(	(0.0)	0/20(0.0)	3/50( 6.0)	1/50(-2.0)	
		0.0			
Terminal rates(c) 0/31( Statistical analysis		0/29( 0.0)	2/29( 6.9)	1/16(6.3)	
reto test Standard method(d) P = Prevalence method(d) P = 0.1556 Combined analysis(d) P =	9991				
Cochran-Armitage test(e) P = 0.5794 Fisher Exact test(e)	5794	P = N.C.	P = 0.1212	P = 0.5000	

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Group Name	Control	250 ppm	1000	4000 num	
	SITE : spleen				
Tumor rate		RIBO			
Overall rates(a)	1/50( 2.0)	0/50(0.0)	9/50(18.0)	3/50( 6 0)	
Adjusted rates(b)	3. 23	0.0	(2) (2) (2) (3) (4)	(5.50)	
Terminal rates(c) Statistical analysis	1/31(3.2)	0/29( 0.0)	5/29(17.2)	2/16(12.5)	
Peto test					
Standard method(d)	± d				
Prevalence method(d)	P = 0.1265				
Cochran-Armitage test(e)					
Fisher fxact test(e)		P = 0.5000	P = 0.0078**	P = 0.3087	
	SITE : Liver TUMON : hemangioma				A STATE OF THE STA
Tumor rate					
Overall rates(a)	2/50(4.0)	2/50(4.0)	5/50(10.0)	3/50(-6.0)	
Adjusted rates(b)	3.23	0.0	7.50	13.04	
Terminal rates(c)	1/31(3.2)	0/29(0.0)	2/29(6.9)	2/16(12.5)	
Statistical analysis Poto test					
Standard method(d)	P = 0 8249				
Prevalence method(d)	P = 0, 0450*				
Combined analysis (d)	P = 0.2212				
Cochran-Armitage test(c)					
Fisher Exact test(e)		P = 0.6913	P = 0.2180	P = 0, 5000	
	SITE : liver				
Tumor rate	Participant of the second of t				
Overall rates(a)	9/50(18.0)	14/50 (28.0)	10/50(20.0)	2/50( 4.0)	
Adjusted rates(b)	25.81	41.38	30.00	7.69	
Terminal rates(c) Statistical analysis	8/31(25.8)	12/29(41.4)	8/29(27.6)	1/16(6.3)	
Peto test					
Standard method(d)	P =				
Prevalence method(d)	P = 0.9834				
combined analysis(d) Cochran-Armitage test(e)	P = 0.0043**				
Fisher Exact test(a)		0.171.0 - 0	( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( )		

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Group Name	Control	250 ppm	1000	4000 yrm	
	SITE : liver TUMOR : histionarie sarrenna				
Tumor rate Overall rates(a)	5/50(10.0)	1/50( 2.0)	1/50( 2.0)	1/50(-2.0)	
Adjusted rates(b) Terminal rates(c)	5.26 1/31(-3.2)	0.0 0/29( 0.0)	0.0 0/29(0.0)	0.0 0/16( 0.0)	
Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysis(d) Ochran-Armiage test(e)	P = 0.5823 P = 0.9227 P = 0.7689 P = 0.788				
Fisher Exact test(e)		P = 0.1022	P = 0.1022	P = 0.1022	
•	SITE : liver TUMOR : hepatocellular carcinoma				
Overall rates(a)	7/50( 14. 0)	15/50( 30.0)	5/50(10.0)	2/50( 4.0)	
Adjusted rates(b)  Terminal rates(c)	15. 63 4/31( 12. 9)	32.35 9/29(31.0)	13.79 4/29( 13.8)	12.50 2/16( 12.5)	
Peto test Standard method(d) Provalence method(d)	P = 0.8807 $P = 0.08007$				
Combined analysis (d) Cochran-Armitage test(e)	P = 0.9877 P = 0.0073**				
Fisher Exact test(e)		P = 0.0448*	P = 0.3798	P = 0.0798	
	SITE : liver TUMOR : hemangioma,hemangiosarcoma				
Tumor rate Overall rates(a)	2/50 ( 4.0)	3/50 ( 6.0)	7/50 (14.0)	4/50(8.0)	
Adjusted rates(b) Terminal rates(c) Statistical analysis	3. 23 1/31( 3. 2)	3.45 1/29(3.4)	10.34 3/29(10.3)	18.75 3/16( 18.8)	
Peto test Standard mcthod(d) Provalence method(d) Combined analysis(d) Cochran-Armitame test(e)	P = 0.8021 P = 0.0248* P = 0.1437 P = 0.6531				
Fisher Exact test(e)		P = 0.5000	P = 0 0798	0380 0 = 0	

Group Name	Control	250 թթա	1000 թթո	4000 µpm	
	SITE : liver				
F	TOWOK · Reparocellular adenoma, Reparocellular carcinoma	hepatocellular carcinoma			
lumor rate					
Overall rates(a)	15/50(30.0)	24/50 (48.0)	13/50 (26.0)	4/50(8.0)	
Adjusted rates(b)	37.50	58.62	36.67	18.75	
Terminal rates(c)	11/31(35.5)	17/29 (58.6)	10/29 (34.5)	3/16(18.8)	
Statistical analysis					
Peto test					
Standard method(d)	P = 0.8807				
Prevalence method(d)	P = 0.9963				
Combined analysis(d)	P = 0.9984				
Cochran-Armitage test(e)	P = 0.0001**				
Fisher Exact test(e)		P = 0.0502	P = 0.4120	P = 0.0047**	
	SITE : epididymis TUMOR : histiocytic sarcoma				
Tumor rate					
Overall rates(a)	1/50( 2.0)	1/50(2.0)	3/50(6.0)	1/50( 2.0)	
Adjusted rates(b)	0.0	3.45	06.9	0.0	
Terminal rates(c)	0/31(0.0)	1/29(3.4)	2/29(6.9)	0/16(0.0)	
Statistical analysis Peto test					
Standard method(d)	P = 0.2543				
Prevalence method(d)	P = 0.5152				
Combined analysis (d)	P = 0.3570				
Conference American tours (a)	0 - 0 - 0				
Fisher Fyact tost (a)	0.0503	D = 0 7595	20000	0 = 0	
(a) read toward toward			r - 0.500	$\Gamma = 0.025$	

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: 0685 : MOUSE B6D2F1/Crlj[Crj:BDF1] : MALE

STUDY No. ANIMAL SEX

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PAGE:

Group Name	Control	250 ppm	muu 1000	4000 ррт	
	SITE : Harderian gland THMOR : adenoma				The state of the s
Cumor rate					
Overall rates(a)	4/49(8.2)	2/50(4.0)	1/50(-2.0)	1/50( 2 0)	
Adjusted rates(b)	12, 12	6.90	3. 45	75.62	
Terminal rates(c)	3/31( 9.7)	2/29(6.9)	1/29(3,4)	0/18( 0 0)	
Statistical analysis					
Peto test					
Standard method(d)	E = C				
Prevalence method(d)	P = 0.7661				
Combined analysis(d)	P =				
Cochran-Armitage test(e)	P = 0.2532				
Fisher Exact test(e)		P = 0.3292	P = 0.1748	P = 0.1748	
HPT360A)					RATSA
					10.00

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis

Prevalence method : Incidental tumor test

Combined analysis: Destin analysis + Incidental tumor test

(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.

?: The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.

?: The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.

Significant difference: \*: P \( \leq \) 0.05 \*\*: P \( \leq \) 0.01

N.C. :Statistical value cannot be calculated and was not significant.

NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	
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Group Name	Control	250 ppm	1000 mag	4000 թրա	
	SITE : ALL SITE TUMOR : hemangioma				
Tumor rate					
Overall rates(a)	3/50( 6.0)	2/50(-4.0)	10/50( 20.0)	6/50(12.0)	
Adjusted rates(b) Terminal rates(c)	6.45	0.0	20.00	25.00	
Statistical analysis	7,51( 0.5)		5/29( 11.2)	4/16(25.0)	
reto test Standard method(d)	P = 0.8249				
Decidar method (4)	D = 0.0235				
Frevalence method(d)	7 = 0.0109* 8 = 0.0616				
Cochran-Armitage test(e)	P = 0.0010				
Fisher Exact test(e)		P = 0.5000	P = 0.0357*	P = 0.2435	
	SITE : ALL SITE				
Tumor rate	omoo ibs ora footastii . wowoi				
Overall rates(a)	8/50(16.0)	3/50(6.0)	7/50 (14.0)	3/50(6.0)	
Adjusted rates(b)	8.11		13.79		
Terminal rates(c)	2/31(6.5)	2/29(6.9)	4/29(13.8)	1/16(6.3)	
Statistical analysis					
ero rest Standard mothod(d)	D = 0 5967				
Desiral order method (d)	D = 0 5007				
Combined analysis (d)	P = 0 6033				
Conference and the Conference toot (a)	D = 0 9585				
Fisher Exact test(e)		P = 0.0999	P = 0.5000	P = 0.0999	
	SITE : ALL SITE				
	٠.				
Tumor rate					
Overall rates(a)	6/50(12.0)	4/50(8.0)	5/50(10.0)	2/50( 4.0)	
djusted rates(b)	9.68	10.34	13.79		
Terminal rates(c) Statistical analysis	3/31(-9.7)	3/29( 10.3)	4/29(13.8)	1/16(6.3)	
Peto test					
Standard method(d)	P = 0.6003				
Prevalence method(d)	P = 0.0316				
combined analysis(d/ Cochran-Armitage test(e)	F = 0.0915 P = 0.1863				
Fisher Exact test(e)		P = 0.3703	P = 0.5000	P = 0.1343	

ANALYSIS
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NEOPLASTIC

STUDY No. : 0685
ANIMAL : MOUSE BGDZFI/Crlj[Crj:BDF1]
SEX : MALE

PAGE:

Group Name	Control	250 µpm	unta 0001	4000 µpm	management of the state of the
Tumor rate Overall rates(a) Adjusted rates(b) Terminal rates(c) Statistical analysis Peto test Standard method(d) Prevalence method(d) Combined analysisical	SITE : ALL SITE  TUMOR : hemangiosarccoma  0/50( 0.0)  0.0  0/31( 0.0)  P = 0.2713  P = 0.2713  P = 0.1989  P = 0.187	1/50( 2.0) 3.45 1/29( 3.4)	4/50( 8.0) 10.34 3/29( 10.3)	1/50( 2.0) 6.25 1/16( 6.3)	
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.923	P = 0.5000	P = 0.0587	P = 0.5000	
(HPT360A)					BATSA

(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.
 ? The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
 . There is no data which should be statistical analysis.
 Significant difference: \* : P ≤ 0.05 \*\* : P ≤ 0.01
 N.C. Statistical value cannot be calculated and was not significant.

#### TABLE O 2

## NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS: FEMALE

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Group Name					
	Control	250 րբա	1000 pm	4000 µµm	
	SITE : lung TUMOR : bronchiolar—alveolar adenoma	ar adonoma			
Tumor rate Overall rates(a)	1/50( 2.0)	3/50(6.0)	1/50( 2.0)	2/50( 4.0)	
Adjusted rates(b) Terminal rates(c)	2. 63 0/23( 0.0)	7.50 0/25(0.0)	4.00 1/25( 4.0)	5.71 2/35(5.7)	
Statistical analysis Peto test Standard method(d)					
rrevalence method(d) Combined analysis(d)	P = 0.4889 P = D = 0.8830				
Coomen Armicage test(e) Fisher Exact test(e)	r - 0.0360	P = 0.3087	P = 0.7525	P = 0.5000	
	SITE : lung TUMOR : bronchiolar-alveol	: lung : bronchiolar-alveolar adenoma bronchiolar-alveolar carcinoma			
Overall rates(a)	1/50( 2.0)	4/50(8.0)	2/50( 4.0)	3/50(6.0)	
Adjusted rates(b) Terminal rates(c)	2. 63 0/23( 0.0)	7.50 0/25(0.0)	4.00 1/25( 4.0)	8.57 3/35(8.6)	
Statistical analysis Peto test					
Standard method(d) Prevalence method(d)	P = 0.6699 P = 0.2868				
Combined analysis(d) Cochran-Armitage test(e)	P = 0.4082 P = 0.7028				
Fisher Exact test(e)		P = 0.1811	P = 0.5000	P = 0.3087	
	SITE : lymph node TUMOR : malignant lymphoma				
Tumor rate Overall rates(a)	18/50(36.0)	20/50 (40.0)	17/50 (34.0)	15/50(30.0)	
Adjusted rates(b)	17.39	28.00	20.00	28.57	
Terminal rates(c) Statistical analysis	4/23(17.4)	7/25(28.0)	5/25 ( 20. 0)	10/35( 28.6)	
Standard method (d)	P = 0.9970				
Prevalence method(d) Combined analysis(d)	P = 0.2508 P = 0.9576				
Cochran-Armitage test(e) Fisher Exact test(e)	P = 0.3586	P = 0.4185	P = 0.5000	P = 0.3355	

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SITE   subject	Group Name	Control	250 րրա	1000 Turk	4000 upan	
0/50( 0.0)   1/30( 2.0)   1/30( 2.0)   1/30( 2.0)   1/30( 2.0)   1/30( 0.0)   1/3		,				
1,50 ( 0, 0)   1,50 ( 2, 0)   1,25 ( 4, 0)   1,25	umor rate					
P = 0.823	Overall rates(a)	0/50(0.0)			0/50(0.0)	
P = 0,8237   0.0)   L/25( 4.0)   L/25( 6.0)   L/25( 6.0	Adjusted rates(b)	0.0			0.0	
P = 0.8237  SITE : spleon TUMON : hearingtocarcoma  0/500 0.0  1/25 ( 4.0)  P = 0.2475  P = 0.1212  P = 0.5000  P = N.C.  1/25 ( 4.0)  P = 0.500  0/500 0.0  1/25 ( 4.0)  P = 0.8377  P = 0.8377  SITE : liver TUMON : hepstocellular adenoma  4/50 ( 8.0)  4/50 ( 8.0)  5/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  6/50 ( 6.0)  7/50 ( 8.0)	<pre>[erminal rates(c) tatistical analysis</pre>	0/23( 0.0)			0/35( 0.0)	
P = 0.7389   P = 0.9088   Street   P = 0.2576   P = 0.1212   P = 0.5000   P = M.C.	eto test					
1	Standard method(d)	P = 0.8237				
SITE : splean  TUMON : hemangioum, hemangicsarcoma  O/50( 0.0)  O/50( 0.0)  O/20( 0.0)  O/	Frevalence method(d) Combined analysis(d)	P = 0.7389				
SITE : spleen TUMOR : hemongious, hemongiosarcoma  0/50( 0.0) 0/20( 0.0) 0/20( 0.0) 1/25( 4.0) 1/25( 4.0) 1/25( 4.0) 0/35( 0/20( 0.0) 0/35( 1/25( 4.0) 1/25( 4.0) 0/35(	contan-Armitage test(e)	P = 0.2676				
SITE : spleen  TUMOR : hemanglocatcoma  0/50( 0.0)	isher Exact test(e)				H	
Decision   Control   Con			College			
0,50( 0.0)	mor rate		2000			
D	verall rates(a)	0/20(0.0)		3/50(6.0)	0/20(-0.0)	
D	djusted rates(b)	0.0		8.00	0.0	
P = 0.3471 P = 0.8620 I) P = 0.8587 st (a) P = 0.8587 SITE : liver TUMOR : hepatocellular adenoma  4/50( 8.0) 2/23( 8.7) P = 0.2475 P = 0.1212 P = 0.2475 P = 0.1212	erminal rates(c)	0/23(0.0)			0/35( 0.0)	
P = 0.3471  P = 0.8620  I) P = 0.8587  st (a) P = 0.3844  P = 0.2475  P = 0.2475  P = 0.1212  P = N.C.  13.79  4/50( 8.0)  3/50( 6.0)  3/50( 6.0)  6/50(  12.00  3/25( 12.0)  9 = 0.9956  10 P = 0.9956  11 P = 0.9956  11 P = 0.9956  12 P = 0.0423*	atistical analysis					
P = 0.3411   P = 0.3820     P = 0.3847     P = 0.3847     P = 0.3847     P = 0.3847     P = 0.2475     P = 0.2475     P = 0.1212     P = N.C.     SITE : liver	eto test Sacaloni contrata	0 1				
1	Standard method(d)	F = 0.34/1 B = 0.650				
SITE : liver TUMOR : hepatocellular adenoma  4/50( 8.0)  2/23( 8.7)  P = 0.2475  P = 0.1212  P = N.C.  13.79  4/50( 8.0)  3/50( 6.0)  0/50(  12.00  2/23( 8.7)  A/25( 16.0)  3/25( 12.0)  0/35(  13.79  P = 0.9956  13.79  P = 0.9956  14.25 ( 16.0)  15.00  16.00  17.00  17.00  18.00  19.00  19.00  10.00	rrevalence method(d)	F = 0.8620				
SITE : liver TUMOR : hepatocellular adenoma  4/50( 8.0)  3/50( 6.0)  3/50( 6.0)  6/35(  13.79  14.25( 16.0)  7/25( 12.0)  15.00  16.00  17.00  17.00  18.00  19.00	companied analysis(d)	F = 0.6367				
SITE : liver TUMOR : hepatocellular adenoma 4/50(8.0) 2/23(8.7) 2/23(8.7) 4/50(6.0) 3/50(6.0) 0/50( 12.00 12.00 12.00 12.00 12.00 0/35( 13.0) 12.00 13.50 14/50(8.0) 15.00 15.00 15.00 16.00 17.00 18.00 19.	isher Exact test(e)	0.3027			P = N.C.	
TUMOR: hepatocellular adenoma 4/50(8.0) 3/50(6.0) 0/50( 13.79 13.79 14.25(16.0) 3/25(12.0) 0/35( 15.0) 15.00 16.00 17.00 17.00 18.79 19.00						
4/50(-8.0) $4/50(-8.0)$ $3/50(-6.0)$ $0/50(-6.0)$ $13.79$ $15.00$ $15.00$ $15.00$ $15.00$ $15.00$ $15.00$ $15.00$ $17.00$						
4/50(8.0) $4/50(8.0)$ $3/50(6.0)$ $0/50($ $13.79$ $16.00$ $12.00$ $12.00$ $12.00$ $12.00$ $12.00$ $13.00$ $13.00$ $13.00$ $13.00$ $13.00$ $14.25(16.0)$ $15.00$	mor rate					
13.79 16.00 12.00 12.00 12.00 17.50 12.00 17.50 12.00 17.50 12.00 17.50 12.00 17.50 12.00 17.50 12.00 17.50 12.00 17.50	)verall rates(a)	4/50(8.0)	4/50(8.0)	3/50(6.0)	0/20(0.0)	
2/23(8.7) 4/25(16.0) 3/25(12.0) 0/35(  p =	Adjusted rates(b)	13. 79	16.00	12.00		
1) P = 0.956 1) P = 0.9956 1) P = 1) P = 1) P =	erminal rates(c)	2/23(8.7)	4/25(16.0)	3/25(12.0)		
method(d)	atistical analysis					
P = 0.9956 P = P = 0.0423*	eto test	1				
F = U.9900 P = P = 0.0423*	Standard method(d)					
F = P = 0.0423*	Prevalence method(d)	P=0.9956				
7 = 0.0423*	Combined analysis(d)	F =				
11 C 11	Coolian-Aimicage lest(e) Fichar Evact tast(a)	1				

	4000 ppm		1/50( 2.0) 2.86		P = 0. 1811		3/50( 6.0)	2/35(5.7)	P = 0.3087
STICAL ANALYSIS	mqq 0001		1/50( 2.0) 2.08 0/25( 0.0)		P = 0. 1811		2/50( 4.0)	4.00 1/25( 4.0)	P = 0.5000
NEOPLASTIC LESIONS-INCIDENCE AND STATISTICAL ANALYSIS	250 թթա		0.0 0/50(0.0)		P = 0.0587		1/50( 2.0)	1/25( 4.0)	P = 0.7525
rlj[Grj:BDF1]	Control	SITE : liver TUMOR : histiocytic sarcoma	4/50(8.0) 2.38 0/23(0.0)	0.96	P = 0.4549	SITE : liver TUMOR : hemangiosarcoma	1/50( 2.0)	1/23(4,3)	P = 0, 2237 P = 0, 3524 P = 0, 2290 P = 0, 2219
STUDY No. : 0685 ANIMAL : MOUSE B6D2FL/Crlj[Crj:BDFL] SEX : FEMALE	Group Name	É	Julior 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)	Turney with	Overall rates(a)	Adjusted faces(v) Terminal rates(c) Statistical analysis Peto text	Standard method(d) Prevalence method(d) Combined analysis(d) Cochran-Armitage test(e) Fisher Exact test(e)

6

PAGE:

Tumor rate					
Overall rates(a)	2/50( 4.0)	1/50( 2.0)	3/50(6.0)	5/50(10.0)	
Adjusted rates(b)	4.35	4.00	8.00	8.57	
Terminal rates(c)	1/23(4.3)	1/25( 4.0)	2/25(8.0)	3/35(8.6)	
Statistical analysis					
Peto test					
Standard method(d)	P = 0.4033				
Prevalence method(d)	P = 0.0979				
Combined analysis(d)	P = 0.1161				
Cochran-Armitage test(e)	P = 0.0865				
Fisher Exact test(e)		P = 0.5000	P = 0.5000	P = 0.2180	

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Group Name	Control	250 ppm	1000 mm	4000 ppm	
	SITE : liver TUMOR : hepatocellular adenoma,hepatocellular carcinoma	ypatocollular carcinoma			
lumor rate Overall rates(a)	4/50(8.0)	5/50 (10.0)	3/50(6.0)	1/50(-2.0)	
Adjusted rates(b)	13.79	20.00	12.00	(S) 13 (S) 13	
Terminal rates(c) Statistical analysis	2/23(8.7)	5/25(20.0)	3/25(12.0)	0/35( 0.0)	
leto test Standard method(d)	=				
Prevalence method(d)	P = 0.9787				
Combined analysis(d)	P = D = 0.1190				
Coontain ministage vest(e) Fisher Exact test(e)	0.1129	P = 0.5000	P = 0.5000	P = 0.1811	
	SITE : pituitary gland TUMOR : adenoma				
Overall rates(a)	2/50( 4.0)	0/50(0.0)	5/50 ( 10.0)	4/49( 8 2)	
Adjusted rates(b)	4.35	0.0	12.00	8. 11.	
Terminal rates(c) Statistical analysis Peto test	1/23( 4.3)	0/25( 0.0)	3/25(12.0)	2/35(5.7)	
Standard method(d)	P = 0.2792				
Prevalence method(d) Combined analysis(d)	P = 0.1904 P = 0.1533				
Cochran-Armitage test(e)	P = 0.1897				
Fisher Exact test(e)		P = 0.2475	P = 0.2180	P = 0.3292	
	SITE : uterus TUMOR : histiocytic sarcoma				
Tumor rate Overall rates(a)	8/50(-16, 0)	7/50 ( 14 0)	17/50( 34 0)	12/50( 24 0)	
Adjusted rates(b)	14.29	4:00	28.00	12, 30, 24, 9)	
Terminal rates(c) Statistical analysis	3/23( 13.0)	1/25(4.0)	7/25( 28.0)	4/35(11.4)	
reto lest Standard method(d) Prevalence method(d)	P = 0.4025 P = 0.3987				
Combined analysis (d)	P = 0.3683 P = 0.3584				
cocnran-Armitage test(e)	$\Gamma = 0.3534$	( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( )			

ANALYSIS
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NEOPLASTIC

: 0685 : MOUSE BGD2FL/Crlj[Crj:BDF1] : FEMALE

STUDY No. ANIMAL SEX

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Group Name	Control	250 րբա	1000 ppm	4000 թչու	
	SITE : Harderian gland				
	TUMOR : adenoma				
Tumor rate					
Overall rates(a)	0/50(0.0)	3/50(6.0)	1/50( 2.0)	2/50( 4 0)	
Adjusted rates(b)	0.0	. 38	4.00	7.00 1.07	
Terminal rates(c)	0/23(0.0)	0/25(0.0)	1/25(4,0)	1/35( 2.9)	
Statistical analysis					
Peto test					
Standard method(d)	) =				
Prevalence method(d)	P = 0.3124				
Combined analysis(d)	р =				
Cochran-Armitage test(e)	P = 0.6260				
Fisher Exact test(e)		P = 0.1212	P = 0.5000	P = 0.2475	
(HPT360A)			Water and the second se		BAIS4

(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.

Standard method : Death analysis Prevalence method : Incidental tumor test

Combined analysis: Death analysis 4 Incidental tumor test
Combined analysis: Death analysis 4 Incidental tumor test
(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.

?: The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.
-----: There is no data which should be statistical analysis.
Significant difference: \*: P ≤ 0.05 \*\*: P ≤ 0.01
N.C.:Statistical value cannot be calculated and was not significant.

SITE : ALL SITE  TUMOR : hemangiouma  2/50(4.0) 4.35  1/23(4.3)  1/23(4.3)  P = 1.0000 ? P = 0.7200  3)  SITE : ALL SITE  TUMOR : histiocytic sarcoma  12/50(24.0) 14.29 3/23(13.0)  P = 0.6129  P = 0.6129  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0) 17.39  4/23(17.4)	250 ppm 4/50( 8. 0) 15.38	1000 maja	, , , , , , , , , , , , , , , , , , ,	AAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
SITE : ALL SITE  TUMOR : lemangiouma  2/50( 4. 0)  4.35  1/23( 4. 3)  1/23( 4. 3)  1/23( 4. 3)  P = 0.7200  P = 0.7200  P = 0.7200  SITE : ALL SITE  TUMOR : histiocytic sarcoma  12/50( 24. 0)  P = 0.6129  P = 0.6129  P = 0.3962  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50( 36. 0)  17.39  4/23( 17. 4)	4/50(8.0)		4000 ppm	
1.50 ( 4.0)   4.35	4/50(8.0)			
### ### ##############################	15.38	4/50(-8.0)	9/50( 4 0)	
P = 1.0000 ?  p = 0.7200  p = 0.7200  p = 0.7869  st(e) P = 0.6076  stTE : ALL SITE  TUMOR : histiocytic sarcoma  12/50(24.0)  14.29  3/23(13.0)  P = 0.6129  P = 0.6129  P = 0.3884  st(c) P = 0.3884  st(c) P = 0.3902  stTE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0)  17.39  4/23(17.4)	(0 01 / 10/ 0	1,05( .0.0)	4.08	
P = 1.0000 ?  p = 0.7200  p = 0.7200  p = 0.7200  p = 0.7200  looping it is a companied in the companied in the constant in the constant in the companied in th	3/ 25 ( 12. 0)	3/25( L2.0)	1/35( 2.9)	
1)				
st(e) P = 0.6076  SITE : ALL SITE  TUMOR : histiocytic sarcoma  12/50(24.0)  14.29  3/23(13.0)  P = 0.6129  P = 0.6129  P = 0.3884  st(c) P = 0.3884  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0)  17.39  4/23(17.4)				
SITE : ALL SITE  TUMOR : histiocytic sarcoma  12/50(24.0)  14.29  3/23(13.0)  P = 0.6129  P = 0.2035  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0)  17.39  4/23(17.4)				
SITE : ALL SITE  TUMOR : histiocytic sarcoma 12/50(24.0) 14.29 3/23(13.0) P = 0.6129 P) P = 0.2035 P) P = 0.3884 st(c) P = 0.3902 )) SITE : ALL SITE TUMOR : malignant lymphoma 18/50(36.0) 17.39 4/23(17.4)	P = 0.3389	P = 0.3389	P = 0.6913	
12/50(24.0) 14.29 3/23(13.0) 14.29 3/23(13.0) P = 0.6129 P = 0.2035 D) P = 0.3884 Stf = Surg StT = ALL SITE TUMOR : malignant lymphoma 18/50(36.0) 17.39 4/23(17.4)				
14.29   3/23(13.0)   P = 0.6129   D = 0.2035   P = 0.3884   STE : ALL SITE   TUMOR : malignant lymphoma   18/50(36.0)   17.39   4/23(17.4)	7/50( 14 0)	19/50(38.0)	14/50/ 90 0	
3/23(13.0)  P = 0.6129  P = 0.2035  1) P = 0.3884  st(c) P = 0.3902  2)  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0)  17.39  4/23(17.4)	4.00	70.00.00 28.00	17 17	
P = 0.6129   D = 0.2035   D = 0.3884   St(c)	1/25( 4.0)	7/25( 28.0)	6/35( 17. 1)	
1				
st(c)				
st(e) P = 0.3902  SITE : ALL SITE  TUMOR : malignant lymphoma  18/50(36.0)  17.39  4/23(17.4)				
SITE : ALL SITE TUMOR : malignant lymphoma 18/50(36.0) 17.39 4/23(17.4)				
SITE : TUMOR : 18/50(	P = 0.1540	P = 0.0971	P = 0.4100	
TUMOR : 18/50( 4/23(				
18/50(				
4/23 (	23/50 (46.0)	18/50(36.0)	15/50(30.0)	
	32.00	24.00	28.57	
ralistical analysis Pato tast	8/25 (32.0)	6/25(24.0)	10/35( 28.6)	
mcthod(d)				
Cochran-Armitage test(e) P = 0.2193				
	P = 0.2081	P = 0.5824	P = 0.3355	

ANALYSIS
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Y No. :	OGSS MOUSE B6D2F1/Cr1;[Crj:BDF1]	NEOPLASTIC LESTONS-INCIDENCE AND STATISTICAL ANALYSIS	TSTICAL ANALYSIS		
SEX : FEMALE					PAGE: 4
Сгоир Мате	Сонтго]	250 pm	1000 ապո	4000 pmm	
	SITE : ALL SITE				4444
	TUMOR : hemangiosarcoma				
Tumor rate	,				
()verall rates(a)	1/50( 2.0)	1/50( 2.0)	3/50( 6.0)	3/50( 6 0)	
Adjusted rates(b)	4.35	4.00	4.00		
Terminal rates(c)	1/23(4.3)	1/25(4.0)	1/25(4.0)	2/35( 5.7)	
Statistical analysis					
Standard method(d)	P = 0.2782				
Prevalence method(d)	P = 0.3524				
Combined analysis(d)	P = 0.2616				
Cochran-Armitage test(e)	P = 0.2824				
Fisher Exact test(e)		P = 0.7525	P = 0.3087	P = 0.3087	
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(a): Number of tumor-bearing animals/number of animals examined at the site.
(b): Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c): Observed tumor incidence at terminal kill.
(d): Beneath the control incidence are the P-values associated with the trend test.
Standard method : Death analysis

Prevalence method : Incidental tumor test

Combined analysis: Death analysis + Incidental tumor test

(e): The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates.

?: The conditional probabilities of the largest and smallest possible out comes can not estimated or this P-value is beyond the estimated P-value.

-----: There is no data which should be statistical analysis.

Significant difference: \*: P \( \leq \) 0.05 \*\*: P \( \leq \) 0.01

N.C.:Statistical value cannot be calculated and was not significant.

### TABLE Q 1

# HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER: $B6D2F1/Crlj \ MALE \ MICE$

TABLE Q 1 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER: B6D2F1/Crl; MALE MICE

No. of animals	No. of animals	Incidence	Min Max.
examined	bearing tumor	(%)	(%)
2244			
	48	2.1	0 - 10
	59	2.6	0 - 10
	107	4.8	0 - 14
2245			
	70	3.1	0 - 14
	96	4.3	0 - 14
	166	7.4	0 - 16
2245			
	145	6.5	0 - 18
	157	7.0	0 - 18
	279	12.4	0 - 22
	examined 2244 2245	examined bearing tumor  2244  48 59 107  2245  70 96 166  2245  145 157	examined         bearing tumor         (%)           2244         48         2.1           59         2.6           107         4.8           2245         70         3.1           96         4.3           166         7.4           2245         145         6.5           157         7.0

<sup>45</sup> carcinogenicity studies examined in Japan Bioassay Research Center were used.

Study No.:

0044,0060,0062,0064,0066,0068,0096,0105,0116,0140,0159,0163,0190,0206,0211, 0225, 0243, 0268, 0270, 0279, 0285, 0297, 0319, 0329, 0343, 0348, 0366, 0372, 0402, 0406, 0418, 0422, 0438, 0449, 0458, 0462, 0498, 0515, 0561, 0580, 0611, 0613,

0642, 0676, 0705

## TABLE Q 2

HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER:  $B6D2F1/CrlCrlj\ FEMALE\ MICE$ 

TABLE Q 2 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : B6D2F1/Crlj FEMALE MICE

Organs	No. of animals	No. of animals	Incidence	Min Max.
Tumors	examined	bearing tumor	(%)	(%)
Uterus	2245			
Histiocytic sarcoma		464	20.7	10 - 34

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

Study No.:

 $0044,\,0060,\,0062,\,0064,\,0066,\,0068,\,0096,\,0105,\,0116,\,0140,\,0159,\,0163,\,0190,\,0206,\\0211,\,0225,\,0243,\,0268,\,0270,\,0279,\,0285,\,0297,\,0319,\,0329,\,0343,\,0348,\,0366,\,0372,\\0402,\,0406,\,0418,\,0422,\,0438,\,0449,\,0458,\,0462,\,0498,\,0515,\,0561,\,0580,\,0611,\,0613,\\0642,\,0676,\,0705$ 

## TABLE R 1

CAUSE OF DEATH: MALE

NALMAL : MOUSE B6D2F1/A SEX : MALE Sroup Name Sroup Name Acribund Animal Noribund Animal Lirombosis Lirombosis Lumor d:leukemia tumor d:leukemia tumor d:subcutis tumor d:subcutis tumor d:subiary gl	### MOUSE B6DZF1/Cr1j[Crj:BDF1]  ###################################	250 ppm 21 2 2 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0	21 21 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	(0-105W) 4000 ppm 34 32 2 2 3 21 21 21 0 0 0 0 1	PAGE
cumor d:epididymis	_	0			

## TABLE R 2

CAUSE OF DEATH: FEMALE

Control 250 ppm 100  27 25 2  1m 0 2 1  1 0 0 0  14 15 1  2 0 0  4 0 0  5 0 0  6 0 0  7 0 0  8 0 0  9 0 0	ANIMAL : MOUSE BGD2F1 SEX : FEMALE	: MOUSE BGDZF1/Crlj[Crj:BDF1] : FEMALE			(0-105#)
rm 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Group Name	Control	250 ppm	1000 ppm	
0 0 1 1 0 0 14 15 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0	Number of Dead and Moribund Animal	27	25	25	1.5
0 1 0 14 12 2 0 0 0 0 1 1 1 4 4 6 6 6 6 7 6 7 7 8 7 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9	no microscop confirm	0	2	0	
1 0 0 14 12 0 0 0 1 1 1 0 0 0 4 0 0 0 0 1 1 1 0 0 0 0	thrombosis	0	_	0	
0 14 15 2 0 0 0 4 0 4 6	arteritis	1	0	0	0
14 15 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	hydronephrosis	0	0	1	0
2 0 0 4 H 44 ·	tumor d:leukemia	14	15	10	ما
0 0 4 1 4.	tumor d:subcutis	2	0		
0 4 1 4.0	tumor d:lung	0	-	Т	0
iry 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1	tumor displeen	0	0	_	0
iry 1 0	tumor d:liver	4	0	2	-
4.	tumor d:pituitary	T	0	0	1
-	tumor d:uterus	4	9	6	-
1 0	tumor dimuscle		0	0	0

## **FIGURES**

FIGURE 1	SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE
FIGURE 2	SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE
FIGURE 3	BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE L
FIGURE 4	BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE
FIGURE 5	FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE
FIGURE 6	FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

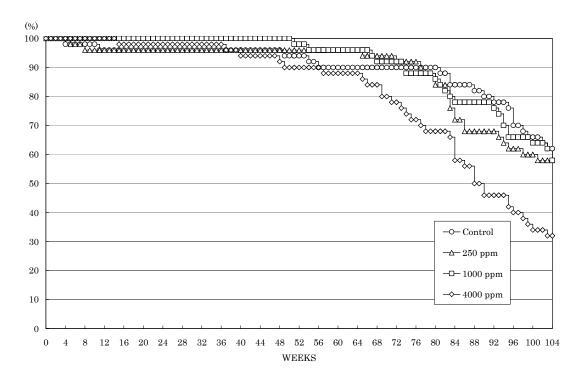


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

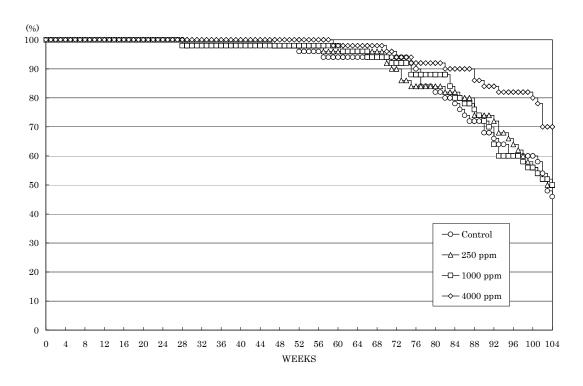


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

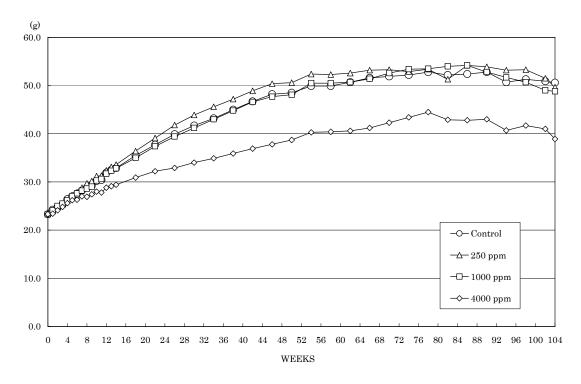


FIGURE 3 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

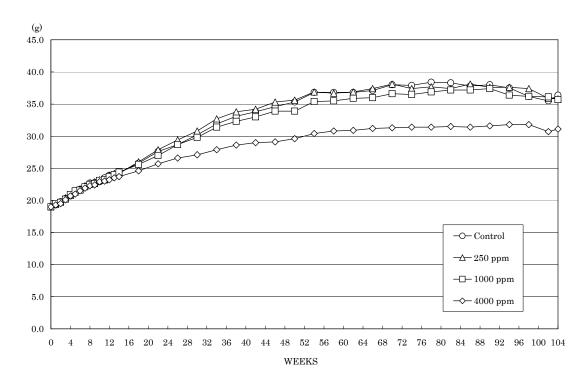


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

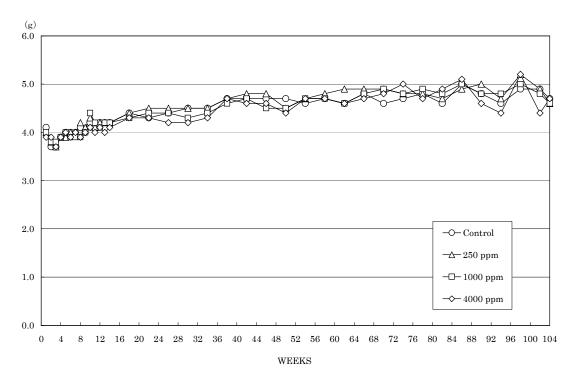


FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE

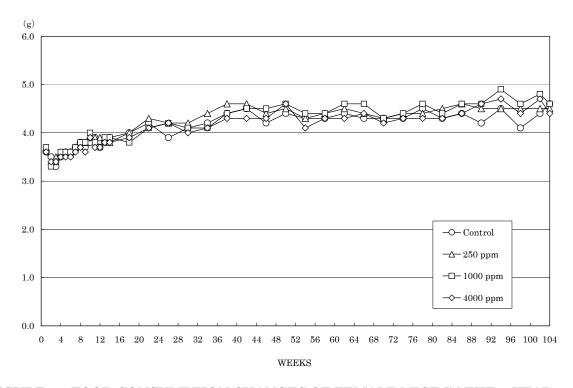
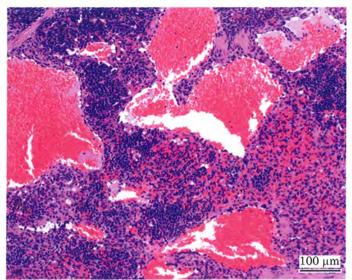
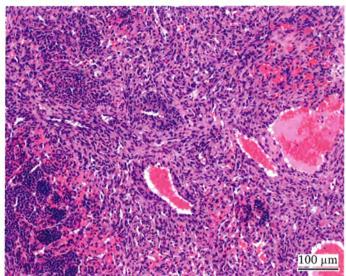


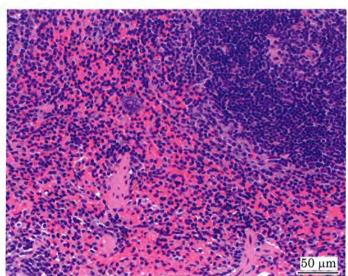
FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR FEED STUDY OF DIPHENYLAMINE



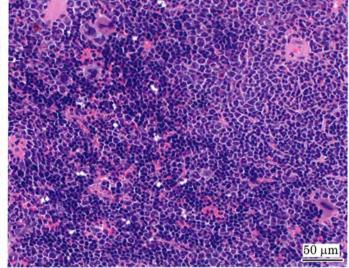
Photograph 1 Spleen: Hemangioma Rat, Male, 1000 ppm, Animal No. 0685-1208 (H&E)



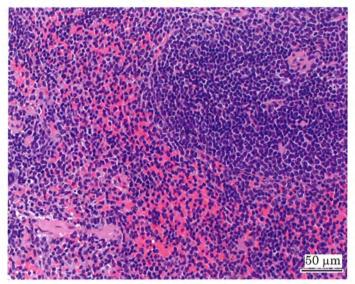
Photograph 2 Spleen: Hemangiosarcoma Rat, Male, 1000 ppm, Animal No. 0685-1222 (H&E)



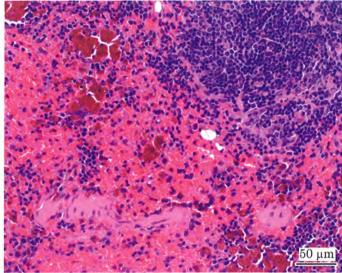
Photograph 3 Spleen: Normal Rat, Male, Control, Animal No. 0685-1004 (H&E)



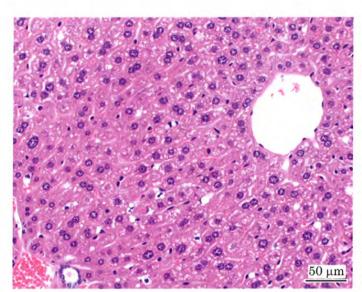
Photograph 4 Spleen: Extramedullary hematopoiesis Rat, Male, 1000 ppm, Animal No. 0685-1202 (H&E)



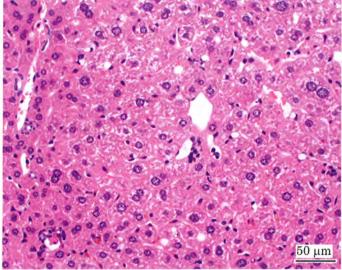
Photograph 5 Spleen: Normal Rat, Female, Control, Animal No. 0685-2002 (H&E)



Photograph 6 Spleen: Engorgement erythrocyte and deposit of hemosiderin Rat, Female, 1000 ppm, Animal No. 0685-2333 (H&E)



Photograph 7 Liver: Normal Rat, Female, Control, Animal No. 0685-2002 (H&E)



Photograph 8 Liver: Hepatocellular hypertrophy Rat, Female, 4000 ppm, Animal No. 0685-2301 (H&E)