Summary of Drinking Water Carcinogenicity Study of Hydrazine Monohydrate Acid in BDF1 Mice

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

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Summary of Drinking Water Carcinogenicity Study of Hydrazine monohydrate in BDF1 Mice

Purpose, materials and methods

Hydrazine monohydrate (CAS No. 7803-57-8) is a colorless clear liquid with a melting point of -51.7°C and with a boiling point of 120.1°C. It is miscible in water, alcohol, and insoluble in chloroform and ether.

The carcinogenicity and chronic toxicity of hydrazine monohydrate (purity : 100% pure) were examined in Crj: BDF1 mice. Groups of test animals were administered hydrazine monohydrate in their drinking water for 2 years (104 weeks). Each group consisted of either 50 male or 50 female mice. The drinking water concentrations of hydrazine monohydrate were 0, 20, 40 or 80 ppm (w/w) for males and 0, 40, 80 or 160 ppm for females. Both sexes were administered each concentration of hydrazine monohydrate. 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 hydrazine monohydrate used in these experiments was confirmed by both infrared spectrometry and mass spectrometry. The chemical was analyzed by infrared spectrometry and high performance liquid chromatography before and after use to affirm its stability. The concentrations of hydrazine monohydrate in the drinking water were determined by high performance liquid chromatography at the time of preparation and on the 4th day after preparation while stored at room temperature. 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 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. Three 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 hydrazine monohydrate 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 study was conducted with reference to the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

Survival rates at the end of the 104 week of the administration period of each groups of both males and females were similar to the respective controls, except males administered 40 and 80 ppm and females administered 40 ppm which were slightly higher than the controls. Body weights, water consumption and food consumption were suppressed dose-dependently throughout most of the 2-year administration period.

The incidences of selected neoplastic lesions of male and female mice are presented in the tables below. The incidence of hepatocellular adenomas was increased and the incidence of hepatocellular carcinomas was marginally increased in female mice. No significant increase in the incidence of neoplastic lesions was found in any hydrazine monohydrate-administered male group as compared with the control. The incidences of hepatocellular adenomas and hepatocellular carcinomas in male mice and adenomas in pituitary in female mice was decreased. As non-neoplastic lesions, desquamation in pelvis in the kidney was increased in males. In the nasal cavity, eosinophilic change in the respiratory epithelium and metaplasia in the respiratory epithelium in females were increased.

Conclusions

In mice, there was no evidence of carcinogenic activity of hydrazine monohydrate in males. There was some evidence of carcinogenic activity of hydrazine monohydrate in females, based on the increased incidences of hepatocellular adenomas and marginally increased incidences of hepatocellular carcinomas.

Incidences of selected neoplastic lesions of male mice in the 2-year drinking water carcinogenicity study of hydrazine monohydrate

Dose (ppm)		0	20	40	80	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	5	6	2	7		
liver	hemangioma	0	0	4	0		
	hepatocellular adenoma	17	12	8 *	6 **		↓↓
malignant tumor							
lung	bronchiolar-alveolar carcinoma	12	10	4	5		
lymph node	malignant lymphoma	4	3	5	5		
spleen	malignant lymphoma	3	3	0	1		
liver	histiocytic sarcoma	3	4	0	3		
	hemangiosarcoma	3	1	2	2		
	hepatocellular carcinoma	21	14	9 **	4 **		↓↓
	hepatoblastoma	3	0	1	0		

Significant difference

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

Incidences of selected neoplastic lesions of female mice in the 2-year drinking water carcinogenicity study of hydrazine monohydrate

Dose (ppm)		0	40	80	160	Peto test	Cochran-Armitage test
Number of examined animals		50	50	50	50		
benign tumor							
lung	bronchiolar-alveolar adenoma	2	3	4	4		
liver	hemangioma	0	0	1	3	↑↑	↑
	hepatocellular adenoma	5	6	2	14 *	↑↑	↑↑
pituitary	adenoma	10	3 *	3 *	0 **		↓↓
malignant tumor							
lung	bronchiolar-alveolar carcinoma	3	0	2	0		
lymph node	malignant lymphoma	22	14	13 *	7 **		↓↓
spleen	malignant lymphoma	4	6	6	6		
liver	hepatocellular carcinoma	2	2	1	4	↑↑	
	hemangiosarcoma	1	2	0	1		
uterus	histiocytic sarcoma	7	9	9	3		
liver	hemangioma+ hemangiosarcoma	1	2	1	4	↑	
	hepatocellular adenoma＋ hepatocellular carcioma	7	8	3	17 *	↑↑	↑↑

Significant difference

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

TABLES

TABLE 1 EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

	2-year study
<Method of Administration>	
Drinking Water	
<Number of Groups>	
Male 4, Female 4	
<Size of Groups>	
50 males and 50 females of each group	
<Animals>	
Strain and Species	
	Crj:BDF_1 mouse
Animal Source	
	Charles River Japan, Inc.
Duration Held Before Study	
	2 wk
Age When Placed on Study	
	6 wk
Age When Killed	
	110～111wk
<Doses>	
<Male>	0, 20, 40, or 80 ppm
<Female>	0, 40, 80, or 160 ppm
<Duration of Dosing>	
7d/wk for 104wk	
<Animal Maintenance>	
Feed	
	CRF-1 (Oriental Yeast Co., Ltd.)
	Sterilized by γ-ray
	Available *ad libitum*
Water	
	Filtrated and sterilized by ultraviolet ray
	Automatic watering system in duration of quarantine
	Glass bottle in duration of acclimation and administration
	Available *ad libitum*
Animal per Cage	
	Single (stainless steel wire)
Animal Room Environment	
	Barrier system
	Temperature : 24±2℃
	Humidity : 55±10%
	Fluorescent light 12h/d
	15~17 room air changes /h
<Type and Frequency of Observation>	
Clinical Sign	
	Observed 1 per d
Body Weight	
	Weighed 1 per wk for 14 wk
	Weighed 1 per 4wks thereafter
Water Consumption	
	Weighed 1 per wk for 14 wk
	Weighed 1 per 4wks thereafter
Food Consumption	
	Weighed 1 per wk for 14 wk
	Weighed 1 per 4wks thereafter

TABLE 1 (Continued) EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

2-year study
<Hematology> Hematological examination performed on scheduled sacrficed animals. The following measurement parameters were examined; Red blood cell (RBC), Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentrate (MCHC), Platelet, White blood cell (WBC), Differential WBC. <Biochemistry> Biochemistrical examination performed on scheduled sacrficed animals. The following measurement parameters were examined; Total protein, Albumin, A/G ratio, Total bilirubin, Glucose, Total cholesterol Triglyceride, Glutamic oxaloacetic transaminase (GOT), Glutamic pyruvic transaminase (GPT), Lactate dehydrogenase (LDH), Alkaline Phosphatase (ALP), Creatine phosphokinase (CPK), Urea nitrogen, Sodium, Potassium, Chloride, Calcium, Inorganic phosphorus. <Urinalysis> Urinalysis performed on all animals that survived to end of dosing period using fresh urine collection. The following measurement parameters were examined; pH, Protein, Glucose, Ketone body, Occult blood, Urobilinogen. <Necropsy> Necropsy performed on all animals. <Organ Weight> Organ weight measurement performed on scheduled sacrificed animals. The following organs were weighed; adrenal, testis, ovary, heart, lung, kidney, spleen, liver, and brain. <Histopathologic Examination> Histopathologic examination performed on all animals. The following organs were examined; skin, nasal cavity, nasopharynx, larynx, trachea, lung, bone marrow, lymph node, thymus, spleen, heart, tongue, salivary gland, esophagus, stomach, small intestine, large intestine, liver, gall bladder, pancreas, kidney, urinary bladder, pituitary, thyroid, parathyroid, adrenal, testis, epididymis, seminal vesicle, prostate, ovary, uterus, vagina, mammary gland, brain, spinal cord, peripheral nerve, eye, Harderian gland, muscle, bone, other organs/tissues with gross lesions.

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		20ppm			40ppm			80ppm		
	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	24.4 (50)	50/50	24.4 (50)	100	50/50	24.4 (50)	100	50/50	24.4 (50)	100	50/50
1	25.6 (50)	50/50	25.1 (50)	98	50/50	24.6 (50)	96	50/50	23.5 (50)	92	50/50
2	26.8 (50)	50/50	26.3 (50)	98	50/50	25.8 (50)	96	50/50	24.5 (50)	91	50/50
3	27.8 (50)	50/50	26.9 (50)	97	50/50	26.3 (50)	95	50/50	25.2 (50)	91	50/50
4	28.9 (50)	50/50	27.7 (50)	96	50/50	26.8 (50)	93	50/50	25.8 (50)	89	50/50
5	29.9 (50)	50/50	28.2 (50)	94	50/50	27.3 (50)	91	50/50	26.3 (50)	88	50/50
6	31.5 (50)	50/50	29.4 (50)	93	50/50	27.9 (50)	89	50/50	27.2 (50)	86	50/50
7	31.7 (50)	50/50	28.9 (50)	91	50/50	27.9 (50)	88	50/50	26.7 (50)	84	50/50
8	32.7 (50)	50/50	29.7 (50)	91	50/50	28.5 (50)	87	50/50	27.4 (50)	84	50/50
9	33.1 (50)	50/50	30.2 (50)	91	50/50	29.0 (50)	88	50/50	27.5 (50)	83	50/50
10	34.7 (50)	50/50	31.2 (50)	90	50/50	29.6 (50)	85	50/50	27.9 (50)	80	50/50
11	35.4 (50)	50/50	31.9 (50)	90	50/50	30.2 (50)	85	50/50	28.3 (50)	80	50/50
12	36.0 (50)	50/50	32.3 (50)	90	50/50	30.4 (50)	84	50/50	28.4 (50)	79	50/50
13	37.2 (50)	50/50	33.4 (50)	90	50/50	31.0 (50)	83	50/50	28.7 (50)	77	50/50
14	37.6 (50)	50/50	33.4 (50)	89	50/50	31.0 (50)	82	50/50	28.9 (50)	77	50/50
18	41.3 (50)	50/50	36.1 (50)	87	50/50	33.6 (50)	81	50/50	30.8 (50)	75	50/50
22	43.9 (50)	50/50	37.5 (50)	85	50/50	34.4 (50)	78	50/50	31.4 (50)	72	50/50
26	46.0 (50)	50/50	38.7 (50)	84	50/50	35.8 (49)	78	49/50	31.9 (50)	69	50/50
30	47.6 (50)	50/50	40.4 (49)	85	49/50	37.3 (49)	78	49/50	33.0 (50)	69	50/50
34	49.0 (50)	50/50	41.4 (49)	84	49/50	38.2 (49)	78	49/50	33.7 (50)	69	50/50
38	50.7 (50)	50/50	43.2 (49)	85	49/50	39.6 (49)	78	49/50	34.7 (50)	68	50/50
42	52.5 (50)	50/50	44.7 (49)	85	49/50	41.0 (49)	78	49/50	35.5 (50)	68	50/50
46	53.5 (50)	50/50	46.4 (49)	87	49/50	42.7 (49)	80	49/50	37.1 (50)	69	50/50
50	53.6 (50)	50/50	46.7 (49)	87	49/50	43.2 (49)	81	49/50	37.7 (50)	70	50/50
54	54.9 (50)	50/50	47.8 (49)	87	49/50	44.0 (48)	80	48/50	38.6 (50)	70	50/50
58	55.0 (48)	48/50	47.8 (49)	87	49/50	44.0 (48)	80	48/50	38.4 (50)	70	50/50
62	55.3 (48)	48/50	49.0 (49)	89	49/50	44.7 (48)	81	48/50	39.2 (50)	71	50/50
66	55.8 (48)	48/50	48.7 (49)	87	49/50	44.3 (48)	79	48/50	39.1 (50)	70	50/50
70	55.6 (46)	46/50	48.3 (48)	87	48/50	44.4 (47)	80	47/50	38.9 (50)	70	50/50
74	56.2 (46)	46/50	48.8 (47)	87	47/50	45.8 (45)	81	45/50	39.4 (50)	70	50/50
78	56.3 (46)	46/50	49.2 (46)	87	46/50	45.1 (44)	80	44/50	39.7 (48)	71	48/50
82	55.8 (46)	46/50	48.3 (45)	87	45/50	44.5 (43)	80	43/50	39.4 (48)	71	48/50
86	55.1 (45)	45/50	48.2 (44)	87	44/50	44.0 (42)	80	42/50	39.0 (46)	71	46/50
90	54.6 (44)	44/50	47.7 (44)	87	44/50	44.6 (40)	82	40/50	39.0 (46)	71	46/50
94	55.0 (42)	42/50	48.8 (39)	89	39/50	44.3 (38)	81	38/50	39.2 (44)	71	44/50
98	52.5 (40)	40/50	48.0 (39)	91	39/50	44.0 (38)	84	38/50	38.1 (43)	73	43/50
102	51.1 (33)	33/50	45.8 (37)	90	37/50	42.5 (36)	83	36/50	37.0 (41)	72	41/50
104	50.0 (31)	31/50	47.5 (30)	95	30/50	41.4 (36)	83	36/50	35.8 (40)	72	40/50

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

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		40ppm			80ppm			160ppm		
	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	19.6 (50)	50/50	19.6 (50)	100	50/50	19.6 (50)	100	50/50	19.6 (50)	100	50/50
1	20.7 (50)	50/50	20.1 (50)	97	50/50	19.5 (50)	94	50/50	16.6 (50)	80	50/50
2	21.5 (50)	50/50	21.0 (50)	98	50/50	20.6 (50)	96	50/50	17.8 (50)	83	50/50
3	21.6 (50)	50/50	21.4 (50)	99	50/50	21.0 (50)	97	50/50	19.2 (50)	89	50/50
4	22.4 (50)	50/50	22.0 (50)	98	50/50	21.8 (50)	97	50/50	19.9 (50)	89	50/50
5	23.0 (50)	50/50	22.8 (50)	99	50/50	22.3 (50)	97	50/50	20.5 (50)	89	50/50
6	23.9 (50)	50/50	23.1 (50)	97	50/50	22.9 (50)	96	50/50	21.0 (50)	88	50/50
7	24.1 (50)	50/50	23.2 (50)	96	50/50	23.0 (50)	95	50/50	21.3 (50)	88	50/50
8	24.9 (50)	50/50	23.7 (50)	95	50/50	23.3 (50)	94	50/50	21.7 (50)	87	50/50
9	24.8 (50)	50/50	24.1 (50)	97	50/50	23.5 (50)	95	50/50	21.9 (50)	88	50/50
10	25.1 (50)	50/50	24.3 (50)	97	50/50	23.8 (50)	95	50/50	21.9 (50)	87	50/50
11	25.3 (50)	50/50	24.2 (50)	96	50/50	24.0 (50)	95	50/50	22.4 (50)	89	50/50
12	25.9 (50)	50/50	24.6 (50)	95	50/50	24.2 (50)	93	50/50	22.4 (50)	86	50/50
13	26.3 (50)	50/50	24.7 (50)	94	50/50	24.2 (50)	92	50/50	22.3 (50)	85	50/50
14	26.3 (50)	50/50	24.7 (50)	94	50/50	24.0 (50)	91	50/50	22.2 (50)	84	50/50
18	28.5 (50)	50/50	25.6 (50)	90	50/50	24.9 (50)	87	50/50	23.1 (50)	81	50/50
22	30.1 (50)	50/50	26.2 (50)	87	50/50	25.7 (50)	85	50/50	23.4 (50)	78	50/50
26	30.9 (50)	50/50	26.7 (50)	86	50/50	26.0 (50)	84	50/50	23.7 (50)	77	50/50
30	32.1 (50)	50/50	27.2 (50)	85	50/50	26.3 (50)	82	50/50	24.1 (50)	75	50/50
34	33.6 (50)	50/50	28.0 (50)	83	50/50	27.2 (50)	81	50/50	24.3 (50)	72	50/50
38	34.6 (50)	50/50	28.3 (50)	82	50/50	26.9 (50)	78	50/50	24.4 (50)	71	50/50
42	36.0 (50)	50/50	28.9 (50)	80	50/50	27.4 (50)	76	50/50	24.6 (50)	68	50/50
46	37.5 (50)	50/50	29.8 (50)	79	50/50	28.3 (50)	75	50/50	25.1 (50)	67	50/50
50	38.5 (50)	50/50	30.3 (50)	79	50/50	28.3 (50)	74	50/50	24.7 (49)	64	49/50
54	39.2 (49)	49/50	30.7 (50)	78	50/50	28.8 (50)	73	50/50	25.2 (49)	64	49/50
58	39.7 (49)	49/50	30.9 (50)	78	50/50	28.6 (49)	72	49/50	25.1 (49)	63	49/50
62	40.2 (49)	49/50	31.6 (50)	79	50/50	28.8 (49)	72	49/50	25.1 (49)	62	49/50
66	41.0 (49)	49/50	31.7 (50)	77	50/50	29.0 (49)	71	49/50	25.2 (49)	61	49/50
70	40.8 (48)	48/50	31.6 (50)	77	50/50	28.9 (49)	71	49/50	25.0 (49)	61	49/50
74	40.9 (46)	46/50	31.5 (50)	77	50/50	28.8 (48)	70	48/50	24.9 (48)	61	48/50
78	41.8 (44)	44/50	31.8 (50)	76	50/50	29.3 (44)	70	44/50	25.2 (46)	60	46/50
82	40.9 (41)	41/50	31.6 (49)	77	49/50	29.1 (44)	71	44/50	24.8 (45)	61	45/50
86	42.0 (40)	40/50	31.8 (47)	76	47/50	29.4 (42)	70	42/50	25.3 (41)	60	41/50
90	41.7 (36)	36/50	31.4 (45)	75	45/50	29.6 (42)	71	42/50	25.2 (39)	60	38/50
94	41.5 (33)	33/50	31.7 (44)	76	44/50	29.4 (41)	71	41/50	24.5 (35)	59	35/50
98	40.6 (28)	28/50	32.1 (41)	79	41/50	29.4 (34)	72	34/50	24.1 (34)	59	34/50
102	40.0 (27)	27/50	32.0 (41)	80	41/50	28.5 (31)	71	31/50	23.4 (29)	58	29/50
104	39.8 (26)	26/50	31.2 (37)	78	37/50	29.0 (29)	73	29/50	23.6 (23)	59	23/50

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

TABLE 4 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	Control	0/50	0/50	0/50	0/50	1/50	1/48	1/46	7/44	8/50(5/19)
	20ppm	0/50	0/50	0/50	0/49	0/49	1/49	3/45	4/42	4/50(1/20)
	40ppm	0/50	0/50	0/49	0/49	0/48	0/48	0/43	0/40	0/50(0/14)
	80ppm	0/50	0/50	0/50	0/50	0/50	0/50	2/48	2/44	2/50(1/10)
Internal mass										
	Control	0/50	1/50	0/50	0/50	0/50	1/48	6/46	8/44	10/50(6/19)
	20ppm	0/50	1/50	1/50	0/49	1/49	2/49	3/45	2/42	6/50(6/20)
	40ppm	0/50	0/50	0/49	1/49	1/48	4/48	2/43	3/40	8/50(6/14)
	80ppm	0/50	1/50	0/50	1/50	1/50	2/50	2/48	2/44	4/50(4/10)

No. of animals with mass / No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 5 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Time of mass occurrence (week)		0～13	14～26	27～39	40～52	53～65	66～78	79～91	92～104	0～104
External mass										
	Control	0/50	0/50	0/50	0/50	0/50	0/49	1/44	1/35	1/50(1/24)
	40ppm	0/50	0/50	0/50	0/50	0/50	0/50	3/50	5/44	6/50(2/13)
	80ppm	0/50	0/50	1/50	1/50	2/50	2/49	1/44	4/41	5/50(2/21)
	160ppm	0/50	0/50	0/50	0/50	0/49	2/49	2/46	2/36	3/50(2/27)
Internal mass										
	Control	0/50	0/50	0/50	0/50	1/50	5/49	7/44	4/35	9/50(9/24)
	40ppm	0/50	1/50	1/50	1/50	1/50	1/50	5/50	9/44	11/50(5/13)
	80ppm	0/50	0/50	1/50	1/50	2/50	3/49	5/44	7/41	13/50(12/21)
	160ppm	0/50	0/50	0/50	0/50	0/49	3/49	3/46	1/36	4/50(4/27)

No. of animals with mass / No. of survival animals at first week on each period.
(No. of dead and moribund animals with mass / No. of dead and moribund animals)

TABLE 6 WATER CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control Av.WC.	Control No. of Surviv. <50>	20ppm Av.WC.	20ppm % of cont. <50>	20ppm No. of Surviv.	40ppm Av.WC.	40ppm % of cont. <50>	40ppm No. of Surviv.	80ppm Av.WC.	80ppm % of cont. <50>	80ppm No. of Surviv.
1	4.4 (50)	50/50	3.2 (50)	73	50/50	2.4 (50)	55	50/50	1.9 (50)	43	50/50
2	4.0 (50)	50/50	3.0 (50)	75	50/50	2.3 (50)	58	50/50	1.8 (50)	45	50/50
3	4.3 (50)	50/50	2.7 (50)	63	50/50	2.2 (50)	51	50/50	1.9 (50)	44	50/50
4	4.4 (50)	50/50	2.8 (50)	64	50/50	2.2 (50)	50	50/50	1.8 (50)	41	50/50
5	4.4 (49)	50/50	3.2 (50)	73	50/50	2.5 (50)	57	50/50	2.2 (50)	50	50/50
6	4.1 (50)	50/50	2.9 (50)	71	50/50	2.2 (50)	54	50/50	1.8 (50)	44	50/50
7	3.8 (47)	50/50	2.6 (50)	68	50/50	2.0 (50)	53	50/50	1.7 (50)	45	50/50
8	3.8 (49)	50/50	2.4 (50)	63	50/50	2.0 (50)	53	50/50	1.8 (50)	47	50/50
9	3.6 (49)	50/50	2.4 (50)	67	50/50	2.1 (50)	58	50/50	1.7 (50)	47	50/50
10	3.8 (49)	50/50	2.4 (50)	63	50/50	2.1 (50)	55	50/50	1.7 (50)	45	50/50
11	3.5 (50)	50/50	2.4 (50)	69	50/50	2.0 (50)	57	50/50	1.8 (50)	51	50/50
12	3.5 (50)	50/50	2.3 (50)	66	50/50	2.0 (50)	57	50/50	1.7 (50)	49	50/50
13	3.5 (50)	50/50	2.2 (50)	63	50/50	1.9 (50)	54	50/50	1.6 (50)	46	50/50
14	3.5 (50)	50/50	2.1 (50)	60	50/50	1.8 (50)	51	50/50	1.6 (50)	46	50/50
18	3.5 (50)	50/50	2.3 (50)	66	50/50	2.1 (50)	60	50/50	1.7 (50)	49	50/50
22	3.4 (50)	50/50	2.1 (50)	62	50/50	1.8 (50)	53	50/50	1.7 (50)	50	50/50
26	3.4 (50)	50/50	2.4 (50)	71	50/50	2.1 (49)	62	49/50	1.8 (50)	53	50/50
30	3.5 (50)	50/50	2.4 (49)	69	49/50	2.2 (49)	63	49/50	1.9 (50)	54	50/50
34	3.5 (50)	50/50	2.4 (49)	69	49/50	2.2 (49)	63	49/50	1.9 (50)	54	50/50
38	3.7 (50)	50/50	2.6 (49)	70	49/50	2.3 (49)	62	49/50	1.9 (50)	51	50/50
42	3.6 (50)	50/50	2.3 (49)	64	49/50	2.1 (49)	58	49/50	1.8 (50)	50	50/50
46	3.7 (50)	50/50	2.7 (49)	73	49/50	2.4 (49)	65	49/50	2.1 (50)	57	50/50
50	3.9 (50)	50/50	2.7 (49)	69	49/50	2.4 (49)	62	49/50	2.1 (50)	54	50/50
54	3.8 (50)	50/50	2.7 (49)	71	49/50	2.4 (48)	63	48/50	2.1 (50)	55	50/50
58	4.0 (48)	48/50	2.7 (49)	67	49/50	2.5 (48)	63	48/50	2.2 (50)	55	50/50
62	4.1 (48)	48/50	3.1 (49)	76	49/50	2.6 (48)	63	48/50	2.3 (50)	56	50/50
66	4.1 (48)	48/50	2.8 (49)	68	49/50	2.6 (48)	63	48/50	2.1 (50)	51	50/50
70	4.1 (46)	46/50	2.8 (48)	68	48/50	2.6 (47)	63	47/50	2.2 (50)	54	50/50
74	4.1 (45)	46/50	2.8 (47)	68	47/50	2.6 (45)	63	45/50	2.2 (50)	54	50/50
78	4.3 (44)	46/50	3.0 (46)	70	46/50	2.6 (44)	60	44/50	2.2 (48)	51	48/50
82	4.5 (46)	46/50	3.0 (45)	67	45/50	2.8 (43)	62	43/50	2.3 (48)	51	48/50
86	4.5 (44)	45/50	3.2 (44)	71	44/50	2.9 (42)	64	42/50	2.4 (46)	53	46/50
90	4.6 (41)	44/50	3.3 (44)	72	44/50	3.1 (40)	67	40/50	2.6 (46)	57	46/50
94	4.7 (41)	42/50	3.1 (39)	66	39/50	2.9 (38)	62	38/50	2.5 (44)	53	44/50
98	4.9 (39)	40/50	3.2 (39)	65	39/50	2.8 (38)	57	38/50	2.4 (43)	49	43/50
102	5.0 (31)	33/50	2.7 (37)	54	37/50	2.7 (36)	54	36/50	2.3 (41)	46	41/50
104	5.4 (29)	31/50	3.1 (30)	57	30/50	2.8 (36)	52	36/50	2.4 (40)	44	40/50

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

TABLE 7 WATER CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		40ppm			80ppm			160ppm		
	Av.WC.	No. of Surviv. <50>	Av.WC.	% of cont. <50>	No. of Surviv.	Av.WC.	% of cont. <50>	No. of Surviv.	Av.WC.	% of cont. <50>	No. of Surviv.
1	3.9 (50)	50/50	2.3 (50)	59	50/50	1.9 (50)	49	50/50	1.1 (50)	28	50/50
2	3.8 (50)	50/50	2.2 (50)	58	50/50	1.9 (50)	50	50/50	1.4 (49)	37	50/50
3	4.0 (49)	50/50	2.2 (50)	55	50/50	1.9 (50)	47	50/50	1.4 (50)	35	50/50
4	4.2 (50)	50/50	2.3 (50)	55	50/50	2.2 (50)	52	50/50	1.5 (50)	36	50/50
5	4.1 (49)	50/50	2.4 (50)	59	50/50	2.3 (50)	56	50/50	1.6 (49)	39	50/50
6	4.2 (49)	50/50	2.3 (50)	55	50/50	2.2 (50)	52	50/50	1.6 (50)	38	50/50
7	4.0 (48)	50/50	2.2 (50)	55	50/50	2.1 (50)	53	50/50	1.5 (50)	38	50/50
8	4.2 (48)	50/50	2.3 (50)	55	50/50	2.3 (50)	55	50/50	1.4 (50)	33	50/50
9	4.1 (50)	50/50	2.2 (50)	54	50/50	2.1 (50)	51	50/50	1.5 (50)	37	50/50
10	4.1 (49)	50/50	2.2 (50)	54	50/50	2.0 (49)	49	50/50	1.4 (50)	34	50/50
11	4.1 (48)	50/50	2.3 (50)	56	50/50	2.2 (50)	54	50/50	1.6 (50)	39	50/50
12	4.1 (49)	50/50	2.3 (50)	56	50/50	2.2 (50)	54	50/50	1.5 (50)	37	50/50
13	4.0 (49)	50/50	2.4 (50)	60	50/50	2.0 (50)	50	50/50	1.5 (50)	38	50/50
14	4.0 (49)	50/50	2.3 (50)	58	50/50	2.1 (50)	53	50/50	1.5 (50)	38	50/50
18	4.1 (49)	50/50	2.3 (50)	56	50/50	2.1 (50)	51	50/50	1.5 (50)	37	50/50
22	4.0 (49)	50/50	2.3 (50)	58	50/50	2.1 (50)	53	50/50	1.4 (50)	35	50/50
26	4.2 (49)	50/50	2.3 (50)	55	50/50	2.2 (50)	52	50/50	1.6 (50)	38	50/50
30	4.1 (50)	50/50	2.5 (50)	61	50/50	2.2 (50)	54	50/50	1.7 (50)	41	50/50
34	4.0 (50)	50/50	2.4 (50)	60	50/50	2.2 (50)	55	50/50	1.7 (50)	42	50/50
38	4.1 (50)	50/50	2.5 (50)	61	50/50	2.2 (50)	54	50/50	1.7 (50)	41	50/50
42	4.1 (50)	50/50	2.2 (50)	54	50/50	2.0 (50)	49	50/50	1.7 (50)	41	50/50
46	3.7 (49)	50/50	2.5 (50)	68	50/50	2.2 (50)	59	50/50	1.8 (50)	49	50/50
50	4.0 (50)	50/50	2.3 (50)	58	50/50	2.1 (50)	53	50/50	1.7 (49)	42	49/50
54	3.8 (49)	49/50	2.5 (50)	66	50/50	2.3 (50)	61	50/50	1.9 (49)	50	49/50
58	4.0 (49)	49/50	2.3 (50)	58	50/50	2.1 (48)	53	49/50	1.7 (49)	42	49/50
62	3.9 (49)	49/50	2.3 (50)	59	50/50	2.1 (49)	54	49/50	1.6 (49)	41	49/50
66	3.9 (49)	49/50	2.4 (50)	62	50/50	2.1 (49)	54	49/50	1.7 (49)	44	49/50
70	3.9 (48)	48/50	2.5 (50)	64	50/50	2.2 (49)	56	49/50	1.7 (49)	44	49/50
74	4.0 (45)	46/50	2.3 (49)	58	50/50	2.1 (47)	53	48/50	1.7 (48)	42	48/50
78	4.0 (42)	44/50	2.4 (49)	60	50/50	2.3 (44)	58	44/50	1.9 (46)	47	46/50
82	4.1 (40)	41/50	2.5 (49)	61	49/50	2.4 (44)	59	44/50	1.9 (45)	46	45/50
86	4.1 (40)	40/50	2.5 (47)	61	47/50	2.4 (42)	59	42/50	1.9 (41)	46	41/50
90	4.2 (36)	36/50	2.5 (44)	60	45/50	2.5 (42)	60	42/50	2.0 (39)	48	38/50
94	4.4 (33)	33/50	2.7 (44)	61	44/50	2.3 (41)	52	41/50	1.9 (35)	43	35/50
98	4.5 (28)	28/50	2.6 (41)	58	41/50	2.6 (34)	58	34/50	2.0 (34)	44	34/50
102	4.2 (24)	27/50	2.6 (41)	62	41/50	2.4 (31)	57	31/50	1.9 (29)	45	29/50
104	4.3 (26)	26/50	2.8 (37)	65	37/50	2.6 (29)	60	29/50	1.9 (23)	44	23/50

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

TABLE 8 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		20ppm			40ppm			80ppm		
	Av.FC.	No. of Surviv. <50>	Av.FC.	% of cont. <50>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.
1	3.7 (50)	50/50	3.6 (50)	97	50/50	3.6 (50)	97	50/50	3.2 (50)	86	50/50
2	3.8 (50)	50/50	3.7 (50)	97	50/50	3.6 (50)	95	50/50	3.4 (50)	89	50/50
3	3.8 (50)	50/50	3.5 (50)	92	50/50	3.5 (50)	92	50/50	3.4 (50)	89	50/50
4	4.9 (50)	50/50	4.8 (50)	98	50/50	3.4 (50)	69	50/50	3.3 (50)	67	50/50
5	3.9 (50)	50/50	3.6 (50)	92	50/50	3.6 (50)	92	50/50	3.4 (50)	87	50/50
6	4.1 (50)	50/50	3.6 (50)	88	50/50	3.7 (49)	90	50/50	3.6 (50)	88	50/50
7	4.0 (50)	50/50	3.7 (50)	92	50/50	3.6 (50)	90	50/50	3.5 (50)	88	50/50
8	4.1 (50)	50/50	3.8 (50)	93	50/50	3.6 (50)	88	50/50	3.5 (50)	85	50/50
9	4.0 (50)	50/50	3.8 (50)	95	50/50	3.6 (50)	90	50/50	3.5 (50)	88	50/50
10	4.0 (50)	50/50	3.8 (50)	95	50/50	3.6 (50)	90	50/50	3.4 (50)	85	50/50
11	4.0 (50)	50/50	3.8 (50)	95	50/50	3.6 (50)	90	50/50	3.5 (50)	88	50/50
12	4.0 (50)	50/50	3.7 (50)	92	50/50	3.5 (50)	88	50/50	3.4 (50)	85	50/50
13	4.0 (50)	50/50	3.6 (50)	90	50/50	3.5 (50)	88	50/50	3.3 (50)	83	50/50
14	4.0 (50)	50/50	3.7 (50)	92	50/50	3.5 (50)	88	50/50	3.4 (50)	85	50/50
18	4.3 (50)	50/50	3.9 (50)	91	50/50	3.8 (50)	88	50/50	3.7 (50)	86	50/50
22	4.2 (50)	50/50	3.7 (50)	88	50/50	3.5 (50)	83	50/50	3.5 (50)	83	50/50
26	4.3 (50)	50/50	4.0 (50)	93	50/50	3.8 (49)	88	49/50	3.6 (50)	84	50/50
30	4.4 (50)	50/50	4.0 (49)	91	49/50	3.8 (49)	86	49/50	3.7 (50)	84	50/50
34	4.5 (50)	50/50	4.1 (49)	91	49/50	3.9 (49)	87	49/50	3.8 (50)	84	50/50
38	4.4 (50)	50/50	3.9 (49)	89	49/50	3.8 (49)	86	49/50	3.6 (50)	82	50/50
42	4.5 (50)	50/50	4.0 (49)	89	49/50	3.8 (49)	84	49/50	3.7 (50)	82	50/50
46	4.5 (50)	50/50	4.1 (49)	91	49/50	4.0 (49)	89	49/50	3.9 (50)	87	50/50
50	4.8 (50)	50/50	4.4 (49)	92	49/50	4.2 (49)	87	49/50	3.9 (50)	81	50/50
54	4.7 (50)	50/50	4.4 (49)	94	49/50	4.3 (48)	91	48/50	4.0 (50)	85	50/50
58	4.6 (48)	48/50	4.3 (49)	93	49/50	4.2 (48)	91	48/50	3.9 (50)	85	50/50
62	4.7 (48)	48/50	4.5 (49)	96	49/50	4.3 (48)	91	48/50	4.0 (50)	85	50/50
66	4.7 (48)	48/50	4.4 (49)	94	49/50	4.2 (48)	89	48/50	4.0 (50)	85	50/50
70	4.6 (46)	46/50	4.3 (48)	93	48/50	4.2 (47)	91	47/50	3.9 (50)	85	50/50
74	4.5 (46)	46/50	4.2 (47)	93	47/50	4.0 (45)	89	45/50	3.8 (50)	84	50/50
78	4.7 (46)	46/50	4.4 (46)	94	46/50	4.2 (44)	89	44/50	4.0 (48)	85	48/50
82	4.5 (46)	46/50	4.3 (45)	96	45/50	4.2 (43)	93	43/50	3.8 (48)	84	48/50
86	4.5 (45)	45/50	4.2 (44)	93	44/50	4.1 (42)	91	42/50	3.8 (46)	84	46/50
90	4.7 (44)	44/50	4.5 (44)	96	44/50	4.5 (40)	96	40/50	4.0 (46)	85	46/50
94	4.7 (42)	42/50	4.4 (39)	94	39/50	4.2 (38)	89	38/50	4.1 (44)	87	44/50
98	4.5 (40)	40/50	4.4 (39)	98	39/50	4.4 (38)	98	38/50	3.9 (43)	87	43/50
102	4.5 (33)	33/50	4.1 (36)	91	37/50	4.3 (36)	96	36/50	3.8 (41)	84	41/50
104	4.6 (31)	31/50	4.2 (30)	91	30/50	4.1 (36)	89	36/50	3.8 (40)	83	40/50

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

TABLE 9 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		40ppm			80ppm			160ppm		
	Av.FC.	No. of Surviv. <50>	Av.FC.	% of cont. <49>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.
1	3.2 (50)	50/50	3.0 (50)	94	50/50	3.0 (50)	94	50/50	2.3 (50)	72	50/50
2	3.2 (50)	50/50	3.2 (50)	100	50/50	3.2 (50)	100	50/50	2.9 (50)	91	50/50
3	3.1 (50)	50/50	3.1 (50)	100	50/50	3.1 (50)	100	50/50	3.1 (50)	100	50/50
4	3.4 (50)	50/50	3.3 (50)	97	50/50	3.3 (50)	97	50/50	3.1 (50)	91	50/50
5	3.4 (50)	50/50	3.3 (50)	97	50/50	3.3 (50)	97	50/50	3.1 (50)	91	50/50
6	3.6 (50)	50/50	3.5 (50)	97	50/50	3.6 (50)	100	50/50	3.3 (50)	92	50/50
7	3.4 (50)	50/50	3.4 (50)	100	50/50	3.4 (50)	100	50/50	3.2 (50)	94	50/50
8	3.7 (50)	50/50	3.6 (50)	97	50/50	3.6 (50)	97	50/50	3.3 (50)	89	50/50
9	3.6 (50)	50/50	3.6 (50)	100	50/50	3.5 (50)	97	50/50	3.2 (50)	89	50/50
10	3.6 (50)	50/50	3.4 (50)	94	50/50	3.5 (50)	97	50/50	3.2 (50)	89	50/50
11	3.5 (50)	50/50	3.4 (50)	97	50/50	3.4 (50)	97	50/50	3.2 (50)	91	50/50
12	3.7 (50)	50/50	3.5 (50)	95	50/50	3.6 (50)	97	50/50	3.2 (50)	86	50/50
13	3.8 (50)	50/50	3.6 (50)	95	50/50	3.5 (50)	92	50/50	3.2 (50)	84	50/50
14	3.6 (50)	50/50	3.5 (50)	97	50/50	3.4 (50)	94	50/50	3.2 (50)	89	50/50
18	3.9 (50)	50/50	3.6 (50)	92	50/50	3.6 (50)	92	50/50	3.4 (50)	87	50/50
22	3.9 (50)	50/50	3.5 (50)	90	50/50	3.5 (50)	90	50/50	3.3 (50)	85	50/50
26	4.0 (50)	50/50	3.6 (50)	90	50/50	3.6 (50)	90	50/50	3.4 (50)	85	50/50
30	4.0 (50)	50/50	3.7 (50)	92	50/50	3.5 (50)	88	50/50	3.4 (50)	85	50/50
34	4.0 (50)	50/50	3.8 (50)	95	50/50	3.7 (50)	92	50/50	3.4 (50)	85	50/50
38	4.1 (50)	50/50	3.5 (50)	85	50/50	3.4 (50)	83	50/50	3.3 (50)	80	50/50
42	4.1 (50)	50/50	3.6 (50)	88	50/50	3.5 (50)	85	50/50	3.5 (50)	85	50/50
46	4.2 (50)	50/50	3.8 (50)	90	50/50	3.7 (50)	88	50/50	3.6 (50)	86	50/50
50	4.2 (50)	50/50	3.8 (50)	90	50/50	3.8 (50)	90	50/50	3.6 (49)	86	49/50
54	4.3 (49)	49/50	4.0 (50)	93	50/50	3.8 (50)	88	50/50	3.8 (49)	88	49/50
58	4.3 (49)	49/50	4.0 (50)	93	50/50	3.8 (49)	88	49/50	3.5 (49)	81	49/50
62	4.2 (49)	49/50	3.9 (50)	93	50/50	3.7 (49)	88	49/50	3.5 (49)	83	49/50
66	4.1 (49)	49/50	3.9 (50)	95	50/50	3.7 (49)	90	49/50	3.5 (49)	85	49/50
70	4.1 (48)	48/50	3.9 (50)	95	50/50	3.6 (49)	88	49/50	3.4 (49)	83	49/50
74	4.3 (46)	46/50	3.8 (50)	88	50/50	3.5 (48)	81	48/50	3.3 (48)	77	48/50
78	4.4 (44)	44/50	3.9 (50)	89	50/50	3.8 (44)	86	44/50	3.5 (46)	80	46/50
82	4.4 (41)	41/50	3.9 (49)	89	49/50	3.8 (44)	86	44/50	3.5 (45)	80	45/50
86	4.2 (40)	40/50	3.7 (47)	88	47/50	3.7 (42)	88	42/50	3.4 (41)	81	41/50
90	4.6 (36)	36/50	3.9 (45)	85	45/50	4.1 (42)	89	42/50	3.6 (39)	78	38/50
94	4.5 (33)	33/50	3.8 (44)	84	44/50	3.8 (41)	84	41/50	3.5 (35)	78	35/50
98	4.7 (28)	28/50	4.1 (41)	87	41/50	3.8 (34)	81	34/50	3.3 (34)	70	34/50
102	4.5 (27)	27/50	3.8 (41)	84	41/50	3.8 (31)	84	31/50	3.1 (29)	69	29/50
104	4.5 (26)	26/50	3.9 (37)	87	37/50	3.8 (29)	84	29/50	3.2 (23)	71	23/50

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

TABLE 10 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS OF MALE MOUSE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Group Name	Control	20ppm	40ppm	80ppm
SITE : liver				
TUMOR : hepatocellular adenoma				
Tumor rate				
Overall rates(a)	17/50(34.0)	12/50(24.0)	8/50(16.0)	6/50(12.0)
Adjusted rates(b)	50.00	30.00	22.22	15.00
Terminal rates(c)	15/31(48.4)	9/30(30.0)	8/36(22.2)	6/40(15.0)
Statistical analysis				
Peto test				
Standard method(d)	P=0.7369			
Prevalence method(d)	P=0.9995			
Combined analysis (d)	P=0.9996			
Cochran-Armitage test(e)	P=0.0068**			
Fisher Exact test(e)		P=0.1891	P=0.0317*	P=0.0082**
SITE : liver				
TUMOR : hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	21/50(42.0)	14/50(28.0)	9/50(18.0)	4/50(8.0)
Adjusted rates(b)	48.39	27.03	16.67	8.00
Terminal rates(c)	15/31(48.4)	8/30(26.7)	6/36(16.7)	3/40(7.5)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9539			
Prevalence method(d)	P=1.0000			
Combined analysis (d)	P=1.0000			
Cochran-Armitage test(e)	P=0.0001**			
Fisher Exact test(e)		P=0.1041	P=0.0078**	P=0.0001**
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	34/50(68.0)	24/50(48.0)	15/50(30.0)	10/50(20.0)
Adjusted rates(b)	84.38	50.00	33.33	22.50
Terminal rates(c)	26/31(83.9)	15/30(50.0)	12/36(33.3)	9/40(22.5)
Statistical analysis				
Peto test				
Standard method(d)	P=0.9683			
Prevalence method(d)	P=1.0000			
Combined analysis (d)	P=1.0000			
Cochran-Armitage test(e)	P<0.0001**			
Fisher Exact test(e)		P=0.0338*	P=0.0001**	P<0.0001**

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneth 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 be 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

TABLE 11 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS OF FEMALE MOUSE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Group Name	Control	40ppm	80ppm	160ppm
SITE : liver				
TUMOR : hepatocellular adenoma				
Tumor rate				
Overall rates(a)	5/50(10.0)	6/50(12.0)	2/50(4.0)	14/50(28.0)
Adjusted rates(b)	14.81	13.51	5.71	35.71
Terminal rates(c)	3/26(11.5)	5/37(13.5)	1/29(3.4)	8/23(34.8)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5777			
Prevalence method(d)	P=0.0036**			
Combined analysis (d)	P=0.0056**			
Cochran-Armitage test(e)	P=0.0087**			
Fisher Exact test(e)		P=0.5000	P=0.2180	P=0.0198*
SITE : liver				
TUMOR : hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	2/50(4.0)	2/50(4.0)	1/50(2.0)	4/50(8.0)
Adjusted rates(b)	7.69	5.41	2.33.	4.35
Terminal rates(c)	2/26(7.7)	2/37(5.4)	0/29(0.0)	1/23(4.3)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0031**?			
Prevalence method(d)	P=0.7087			
Combined analysis (d)	P=0.1271			
Cochran-Armitage test(e)	P=0.3270			
Fisher Exact test(e)		P=0.3087	P=0.5000	P=0.3389
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	7/50(14.0)	8/50(16.0)	3/50(6.0)	17/50(34.0)
Adjusted rates(b)	22.22	18.92	6.98	38.71
Terminal rates(c)	5/26(19.2)	7/37(18.9)	1/29(3.4)	8/23(34.8)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0192*			
Prevalence method(d)	P=0.0199*			
Combined analysis (d)	P=0.0036**			
Cochran-Armitage test(e)	P=0.0090**			
Fisher Exact test(e)		P=0.5000	P=0.1589	P=0.0169*
SITE : liver				
TUMOR : hemangioma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	1/50(2.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	3.45	8.70
Terminal rates(c)	0/26(0.0)	0/37(0.0)	1/29(3.4)	2/23(8.7)
Statistical analysis				
Peto test				
Standard method(d)	P=0.0879 ?			
Prevalence method(d)	P=0.0217*			
Combined analysis (d)	P=0.0051**			
Cochran-Armitage test(e)	P=0.0168*			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.1212

TABLE 11 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS OF FEMALE MOUSE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

(Continued)

Group Name	Control	40ppm	80ppm	160ppm
SITE : liver				
TUMOR : hemangioma, hemangiosarcoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	2/50(4.0)	1/50(2.0)	4/50(8.0)
Adjusted rates(b)	0.0	2.70	3.45	11.54
Terminal rates(c)	0/26(0.0)	1/37(2.7)	1/29(3.4)	2/23(8.7)
Statistical analysis				
Peto test				
Standard method(d)	P=0.5039			
Prevalence method(d)	P=0.0206*			
Combined analysis (d)	P=0.0578			
Cochran-Armitage test(e)	P=0.1432			
Fisher Exact test(e)		P=0.5000	P=0.2475	P=0.1811

(a):Number of tumor-bearing animals/number of animals examined at the site.
(b):Kaplan-Meire estimated tumor incidence at the end of the study after adjusting for intercurrent mortality.
(c):Observed tumor incidence at terminal kill.
(d):Beneth 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 be 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

TABLE 12 NUMBER OF MICE WITH SELECTED NON-NEOPLASTIC LESIONS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Group name		Male				Female			
		Control	20ppm	40ppm	80ppm	Control	40ppm	80ppm	160ppm
<all animal No.>(sacrificed animal No.)		<50> (31)	<50> (30)	<50> (36)	<50> (40)	<50> (26)	<50> (37)	<50> (29)	<50> (23)
Kidney		0 (0)	0 (0)	4 (3)	12** (11)**	3 (1)	22** (17)**	11* (10)*	6 (4)
desquamation: pelvis	+	0 (0)	0 (0)	1 (1)	6 (5)	3 (1)	11 (8)	7 (6)	4 (2)
	2+	0 (0)	0 (0)	3 (2)	6 (6)	0 (0)	11 (9)	4 (4)	2 (2)
	3+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	4+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal cavity		27 (19)	8** (3)**	9** (5)**	11** (9)**	25 (13)	35 (28)	39* (23)	36* (17)
eosinophilic change:	+	19 (12)	7 (3)	6 (4)	8 (6)	13 (8)	15 (10)	21 (9)	16 (6)
respiratory epithelium	2+	8 (7)	0 (0)	3 (1)	3 (3)	9 (4)	18 (16)	16 (13)	19 (10)
	3+	0 (0)	1 (0)	0 (0)	0 (0)	3 (1)	2 (2)	2 (1)	1 (1)
	4+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal cavity		31 (21)	11** (7)**	9** (8)**	5** (5)**	5 (1)	18** (16)**	21** (14)**	15* (10)**
respiratory metaplasia:	+	12 (8)	8 (5)	8 (7)	3 (3)	5 (1)	14 (12)	12 (7)	15 (10)
gland	2+	16 (11)	3 (2)	1 (1)	2 (2)	0 (0)	4 (4)	9 (7)	0 (0)
	3+	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	4+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Grade +:Slight 2+:Moderate 3+:Marked 4+:Severe
< >:Number of animals examined at the site
( ):Sacrificed animals
Significant difference ; *: P≦0.05 **: P≦0.01 Test of Chi Square

TABLE 13 CAUSE OF DEATH OF MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

		Male				Female			
Group		Control	20ppm	40ppm	80ppm	Control	40ppm	80ppm	160ppm
Number of dead or moribund animals		19	20	14	10	24	13	21	27
No microscopical confirmation		0	2	0	0	0	0	0	8
Hepatic lesion		0	0	0	0	0	1	1	1
Body cavity lesion		0	0	0	0	0	0	1	0
Renal lesion		0	1	1	0	0	0	0	0
Urinary retention		3	0	1	0	0	0	0	0
Arteritis		0	0	1	0	0	0	0	1
Hydronephrosis		0	1	3	0	2	0	1	2
Tumor death	leukemia	1	0	2	3	13	5	10	7
	subcutis	2	0	0	0	0	0	0	0
	lung	4	5	1	1	0	0	0	0
	lymph node	0	0	0	0	0	1	0	0
	spleen	0	0	0	0	0	0	0	1
	tooth	0	0	0	1	0	0	0	0
	liver	8	9	4	3	1	2	2	4
	kidney	0	1	0	1	0	0	0	0
	epididymis	1	0	1	1	0	0	0	0
	uterus	0	0	0	0	7	3	6	2
	spinal cord	0	0	0	0	1	0	0	0
	bone	0	0	0	0	0	1	0	1
	peripheral nerve	0	1	0	0	0	0	0	0

FIGURES

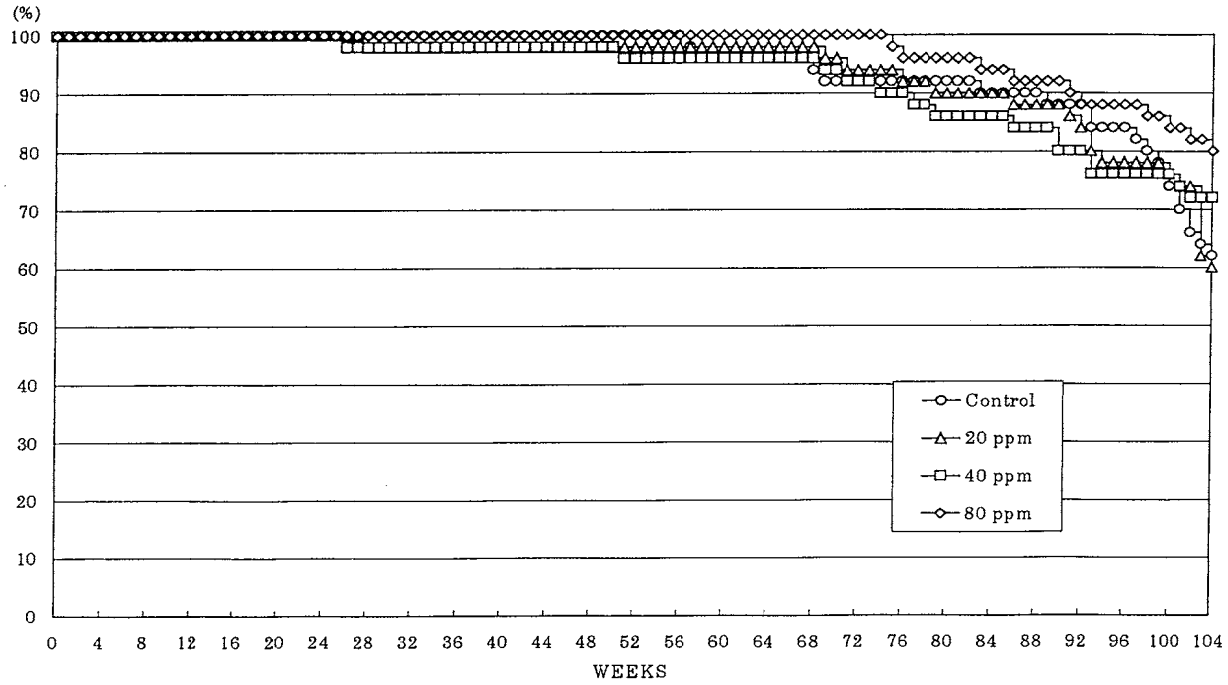


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

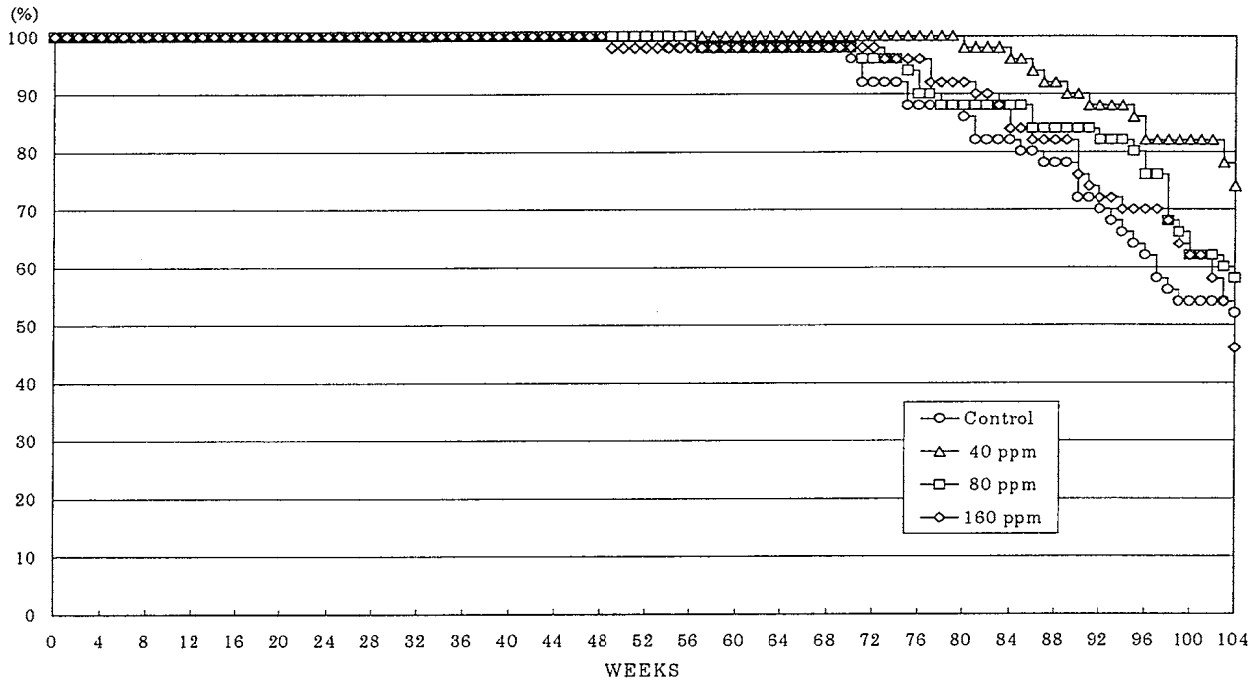


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

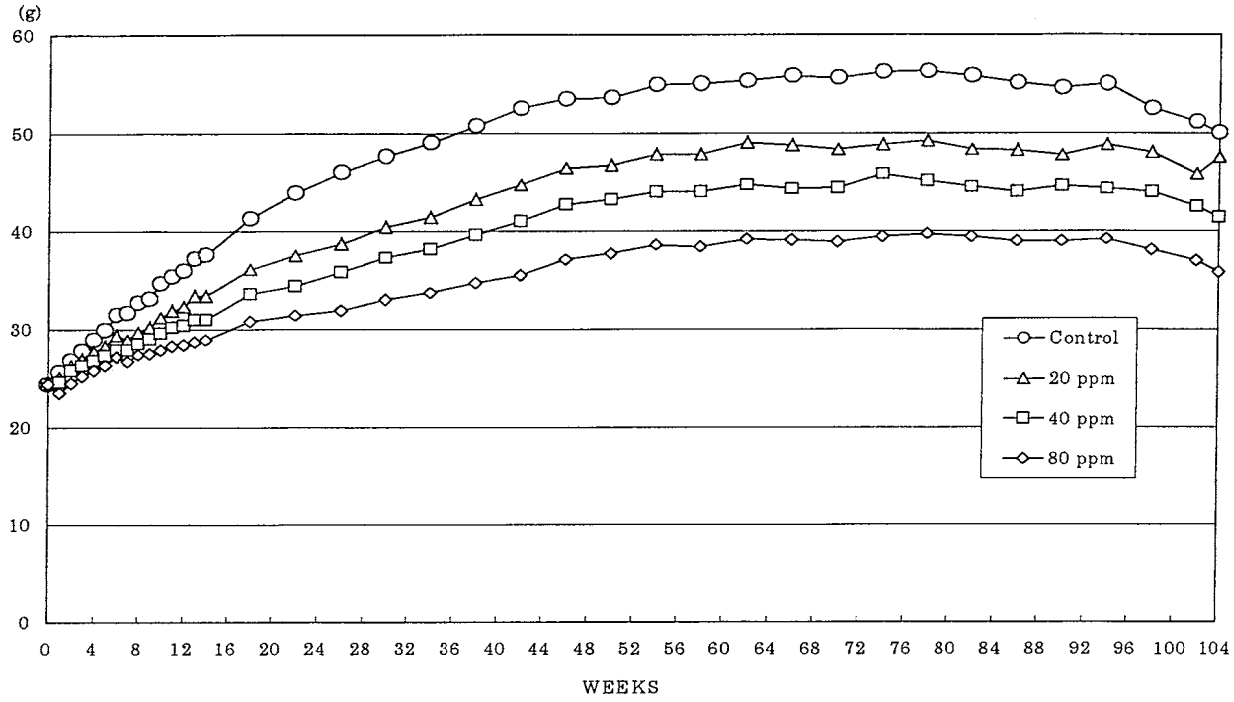


FIGURE 3 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

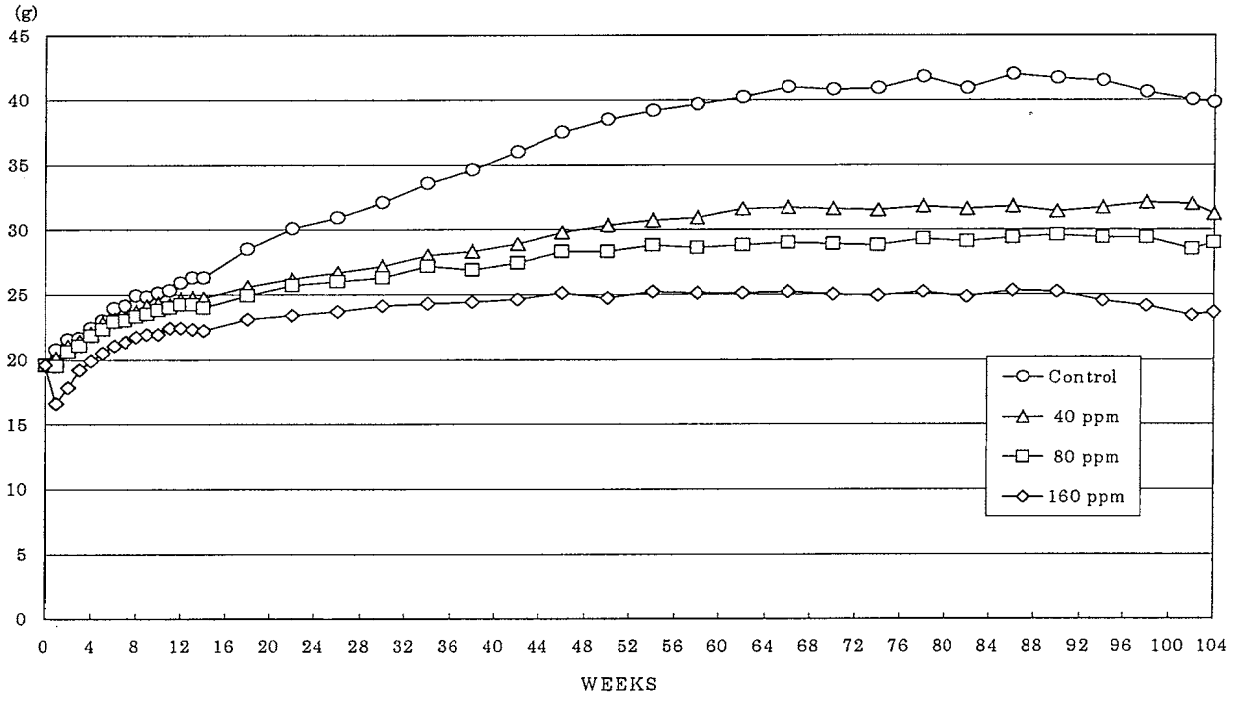


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

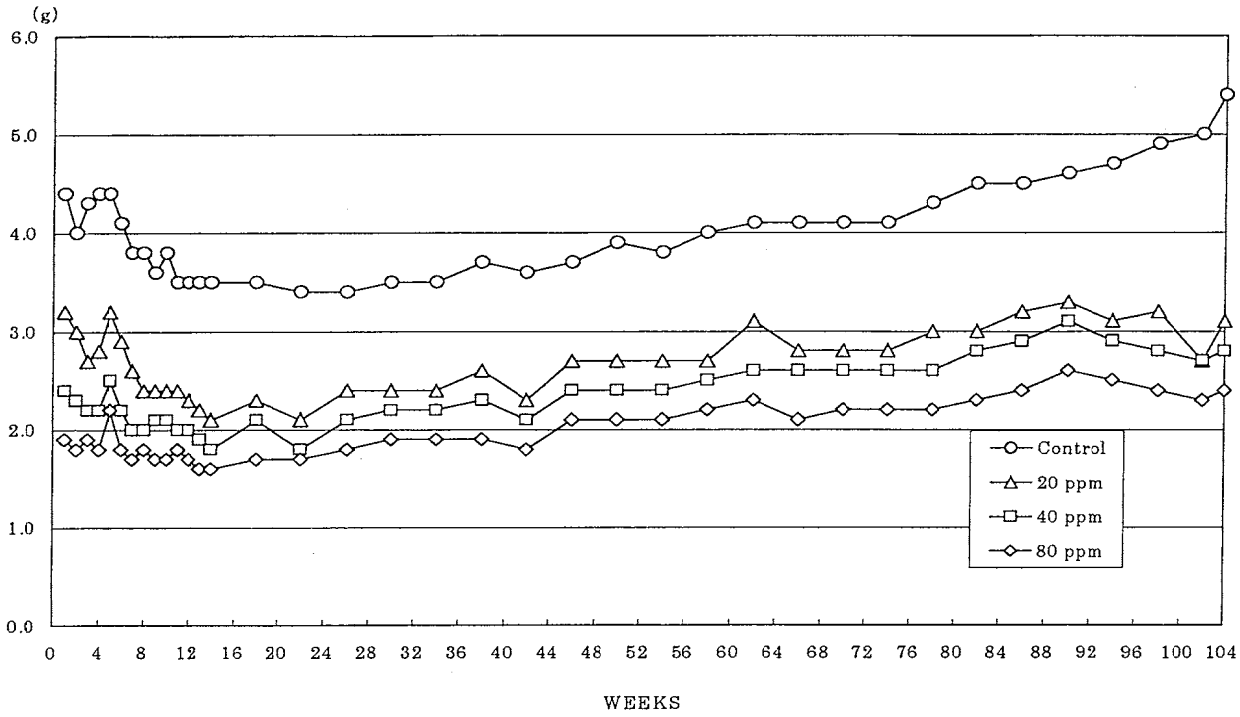


FIGURE 5 WATER CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

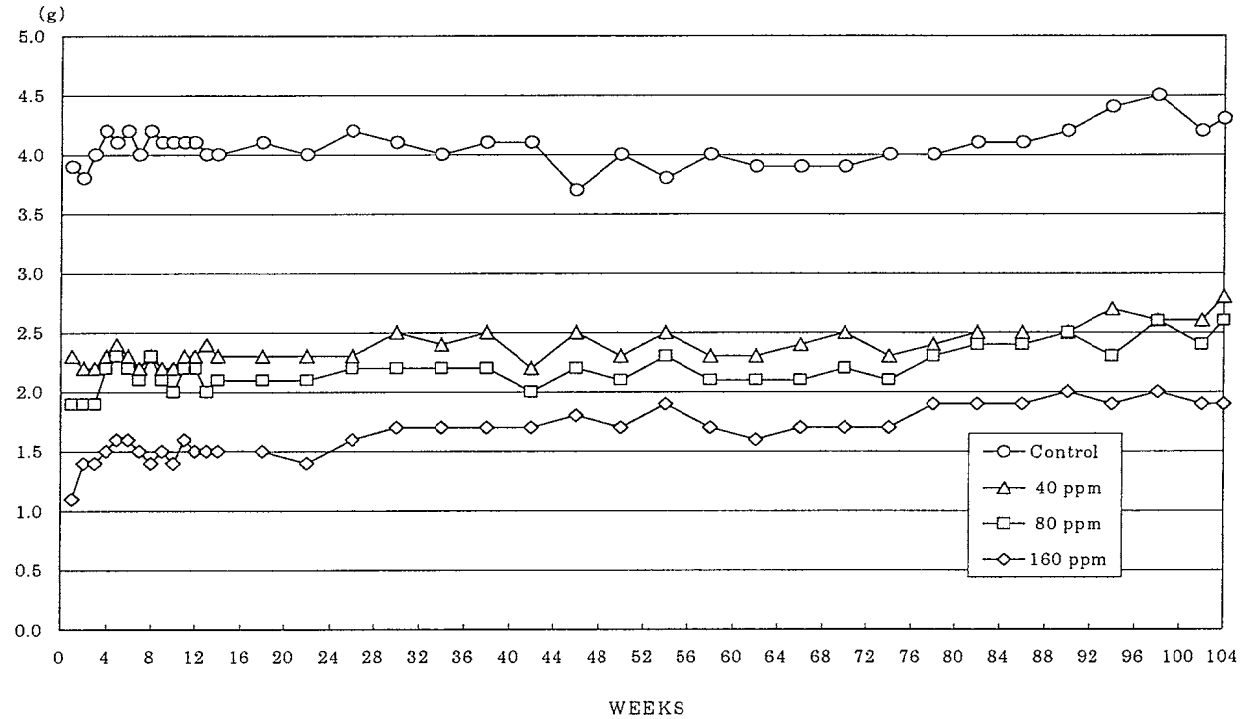


FIGURE 6 WATER CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

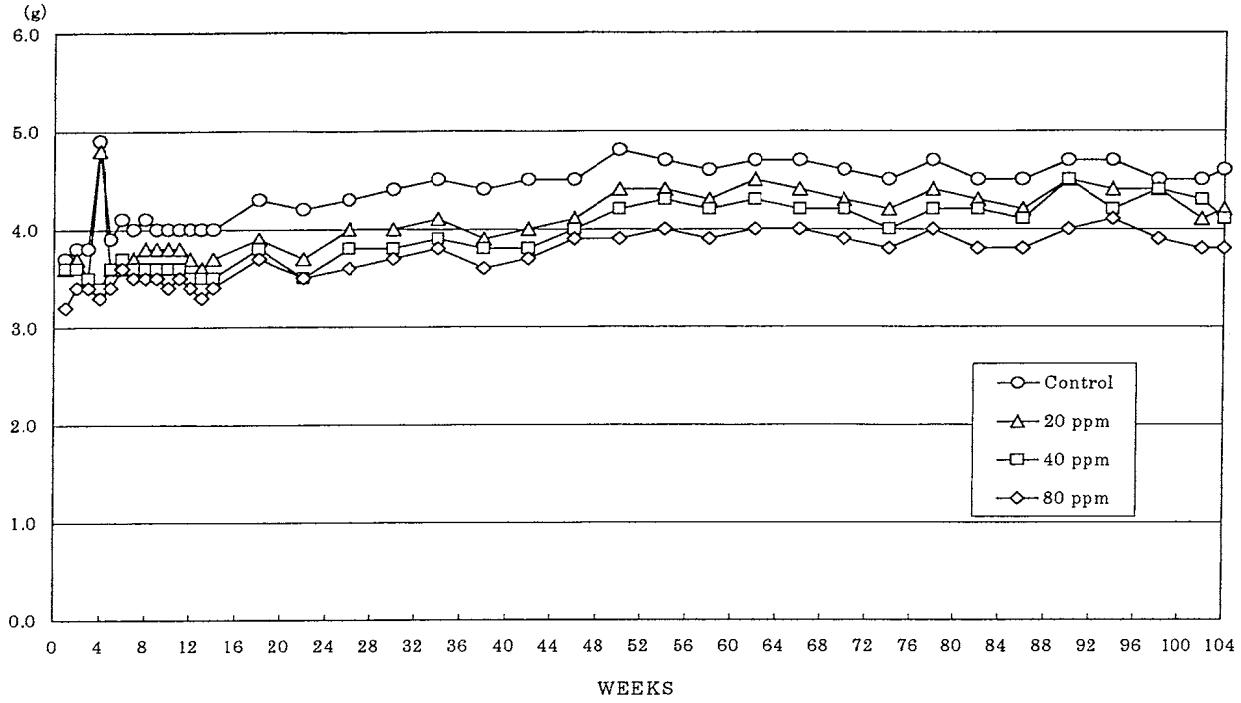


FIGURE 7 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

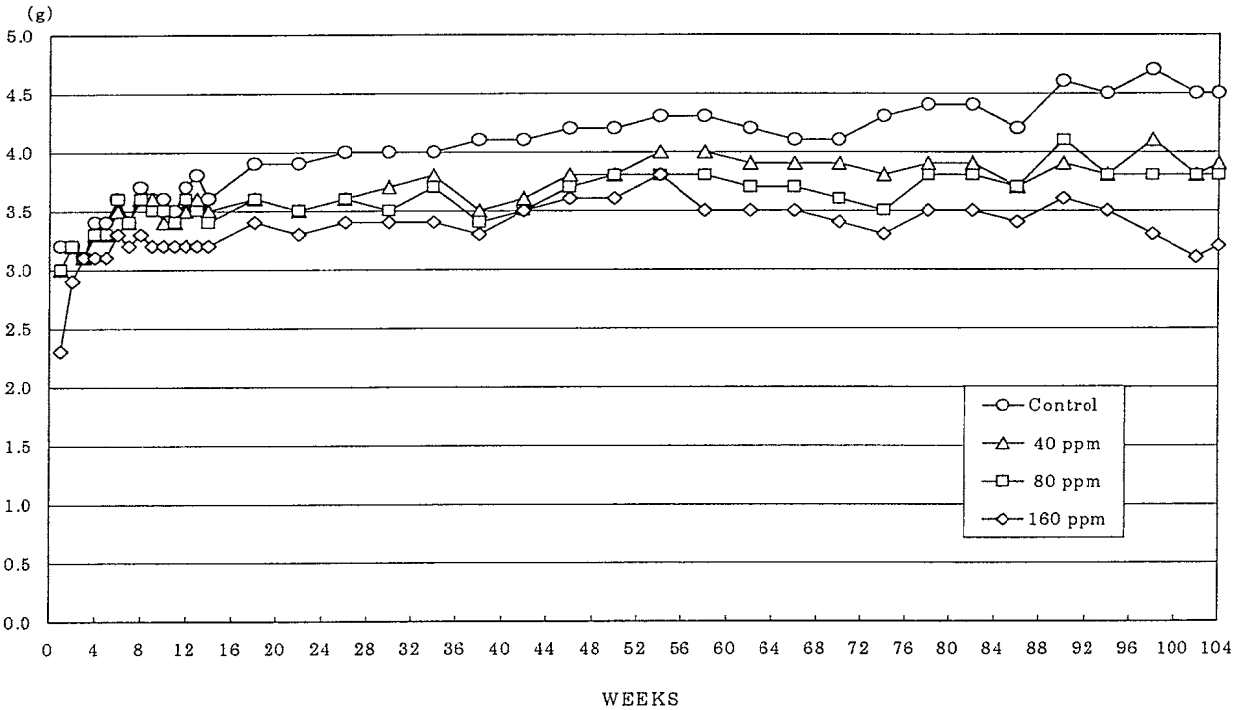


FIGURE 8 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

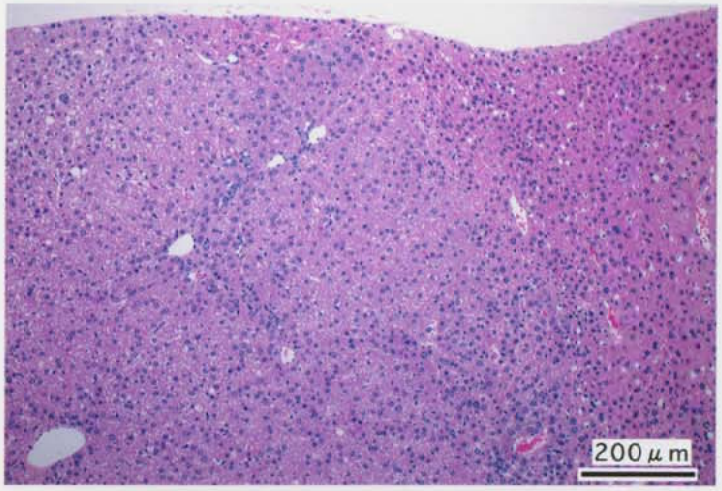
PHOTOGRAPHS

PHOTOGRAPH 1 LIVER: HEPATOCELLULAR ADENOMA,
MOUSE, FEMALE, 160ppm, ANIMAL NO. 0285-2307 (H&E)

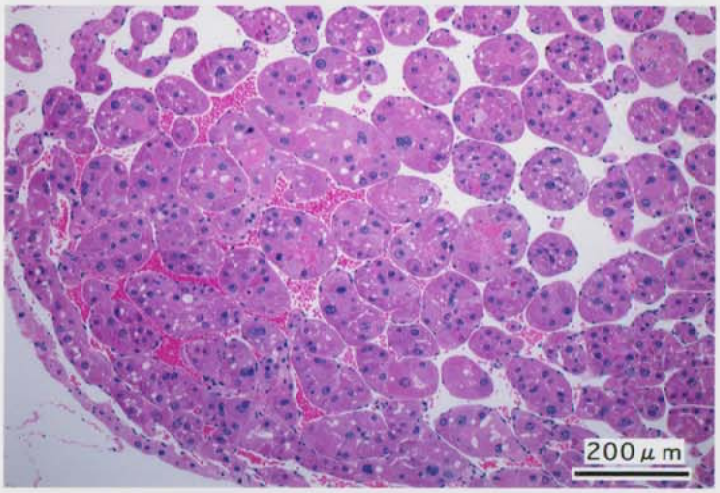
PHOTOGRAPH 2 LIVER: HEPATOCELLULAR CARCINOMA,
MOUSE, FEMALE, 160ppm, ANIMAL NO. 0285-2323 (H&E)

PHOTOGRAPH 3 LIVER: HEMANGIOMA,
MOUSE, FEMALE, 160ppm, ANIMAL NO. 0285-2301 (H&E)

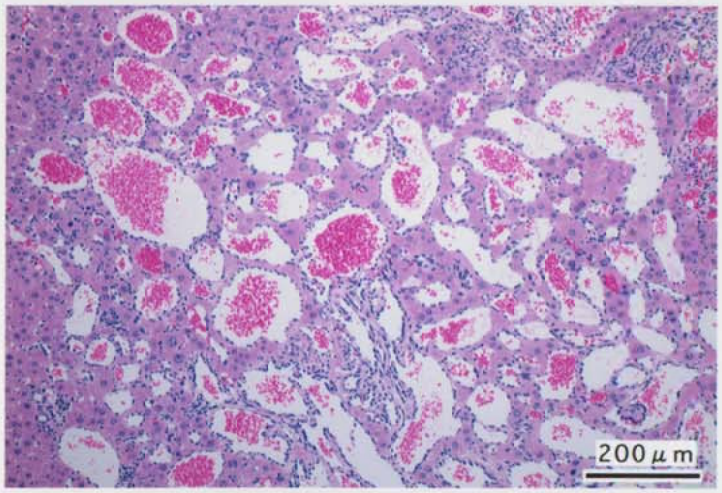
PHOTOGRAPH 4 KIDNEY: DESQUAMATION: PELVIS
MOUSE, MALE, 80ppm, ANIMAL NO. 0285-1301 (H&E)



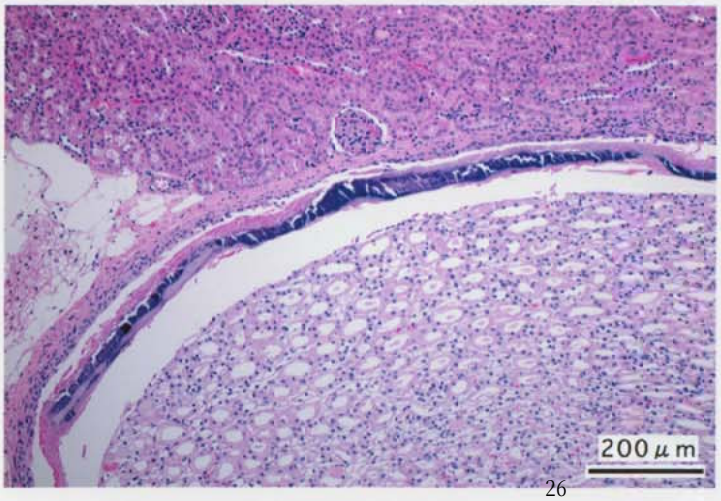
PHOTOGRAPH. 1



PHOTOGRAPH. 2



PHOTOGRAPH. 3



PHOTOGRAPH. 4