Summary of Drinking Water Carcinogenicity Study of Hydrazine Monohydrate in F344 Rats

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Japan Bioassay Research Center

Japan Industrial Safety and Health Association

PREFACE

The tests were contracted and supported by the Ministry of Labour 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 Labour of Japan on December 21, 2000.

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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 F344/DuCrj rats. 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 rats. The drinking water concentrations of hydrazine monohydrate were 0, 20, 40 or 80 ppm (w/w). 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 grops of both males and females were similar to the respective controls, except females administered 80 ppm which was decreased as compared with the control. Red urine was observed in all the hydrazine monohydrate administered female groups. 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 rats are presented in the tables below. The incidences of hepatocellular adenomas was marginally increased as the positive trend by Peto's test and the pre-neoplastic incidence of acidophilic cell foci of the liver was increased in males. The incidences of hepatocellular carcinomas and adenomas was increased as the positive trend by Peto's test and the pre-neoplastic incidence of acidophilic cell foci and basophilic cell foci of the liver was increased in the females.

As non-neoplastic lesions, papillary mineralization, urothelial hyperplasia in pelvis, papillary necrosis and infarct in the kidney was increased in both males and females.

Conclusions

In rats, there was some evidence of carcinogenic activity of hydrazine monohydrate in males, based on the marginally increased incidences of hepatocellular adenomas and increased pre-neoplastic incidence of acidophilic cell foci of the liver. There was some evidence of carcinogenic activity of hydrazine monohydrate in females, based on the increased incidences of hepatocellular carcinomas and adenomas and increased pre-neoplastic incidence of acidophilic cell foci and basophilic cell foci of the liver in the females.

Incidences of selected neoplastic lesions of male rats 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							
subcutis	fibroma	5	7	5	4		
lung	bronchiolar-alveolar adenoma	3	3	3	1		
liver	hepatocellular adenoma	0	0	0	3	↑↑	↑↑
pancreas	islet cell adenoma	1	3	1	2		
pituitary	adenoma	33	21 *	25	21 *		
thyroid	C-cell adenoma	5	7	5	3		
adrenal	pheochromocytoma	8	8	4	6		
testis	interstitial cell tumor	37	45 *	43	44	↑	
malignant tumor							
lung	bronchiolar-alveolar carcinoma	0	3	0	0		
spleen	mononuclear cell leukemia	5	3	1	1		
liver	hepatocellular carcioma	0	0	0	1		
liver	hepatocellular adenoma＋ hepatocellular carcioma	0	0	0	4	↑↑	↑↑

Significant difference

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

Incidences of selected neoplastic lesions of female rats 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							
liver	hepatocellular adenoma	1	0	3	4	↑	
pituitary	adenoma	23	26	23 1)	16		
thyroid	C-cell adenoma	7	2	1 *	2		
uterus	endometrial stromal polyp	7	6	5	4		
adrenal	pheochromocytoma	1	3	0	0		
mammary gland	fibroadenoma	9	8	0 *	2 *		↓↓
malignant tumor							
liver	hepatocellular carcioma	0	0	0	4	↑↑	↑↑
spleen	mononuclear cell leukemia	6	3	1	1		↓
mammary gland	adenocarcinoma	1	0	0	0		
liver	hepatocellular adenoma＋ hepatocellular carcioma	1	0	3	6	↑↑	↑↑

1) : Number of examined animals in pituitary is 48.

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 F344/DuCrj (Fischer) rat 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, 20, 40, or 80 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, Phospholipid, Glutamic oxaloacetic transaminase (GOT), Glutamic pyruvic transaminase (GPT), Lactate dehydrogenase (LDH), Alkaline Phosphatase (ALP), γ-Glutamyl transpeptidase (G-GTP), Creatine phosphokinase (CPK), Urea nitrogen, Creatinine, 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, Bilirubin, 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 per sex per groups. 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, 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 RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control Av.Wt.	Control No. of Surviv. <50>	20ppm Av.Wt.	20ppm % of cont. <50>	20ppm No. of Surviv.	40ppm Av.Wt.	40ppm % of cont. <50>	40ppm No. of Surviv.	80ppm Av.Wt.	80ppm % of cont. <50>	80ppm No. of Surviv.
0	126 (50)	50/50	126 (50)	100	50/50	126 (50)	100	50/50	126 (50)	100	50/50
1	156 (50)	50/50	154 (50)	99	50/50	150 (50)	96	50/50	145 (50)	93	50/50
2	184 (50)	50/50	180 (50)	98	50/50	176 (50)	96	50/50	166 (50)	90	50/50
3	204 (50)	50/50	200 (50)	98	50/50	194 (50)	95	50/50	182 (50)	89	50/50
4	219 (50)	50/50	215 (50)	98	50/50	209 (50)	95	50/50	193 (50)	88	50/50
5	232 (50)	50/50	230 (50)	99	50/50	223 (50)	96	50/50	204 (50)	88	50/50
6	244 (50)	50/50	242 (50)	99	50/50	234 (50)	96	50/50	212 (50)	87	50/50
7	260 (50)	50/50	258 (50)	99	50/50	249 (50)	96	50/50	224 (50)	86	50/50
8	270 (50)	50/50	269 (50)	100	50/50	261 (50)	97	50/50	234 (50)	87	50/50
9	280 (50)	50/50	279 (50)	100	50/50	270 (50)	96	50/50	243 (50)	87	50/50
10	289 (50)	50/50	288 (50)	100	50/50	278 (50)	96	50/50	249 (50)	86	50/50
11	299 (50)	50/50	297 (50)	99	50/50	287 (50)	96	50/50	257 (50)	86	50/50
12	305 (50)	50/50	303 (50)	99	50/50	292 (50)	96	50/50	261 (50)	86	50/50
13	313 (50)	50/50	310 (50)	99	50/50	300 (50)	96	50/50	269 (50)	86	50/50
14	321 (50)	50/50	318 (50)	99	50/50	307 (50)	96	50/50	275 (50)	86	50/50
18	348 (50)	50/50	341 (50)	98	50/50	328 (50)	94	50/50	293 (50)	84	50/50
22	367 (50)	50/50	355 (50)	97	50/50	339 (50)	92	50/50	300 (50)	82	50/50
26	382 (50)	50/50	371 (50)	97	50/50	353 (50)	92	50/50	311 (50)	81	50/50
30	399 (50)	50/50	383 (50)	96	50/50	364 (50)	91	50/50	318 (50)	80	50/50
34	413 (50)	50/50	397 (50)	96	50/50	377 (50)	91	50/50	327 (50)	79	50/50
38	426 (50)	50/50	406 (50)	95	50/50	386 (50)	91	50/50	330 (50)	77	50/50
42	438 (50)	50/50	420 (50)	96	50/50	397 (50)	91	50/50	336 (50)	77	50/50
46	448 (50)	50/50	426 (50)	95	50/50	403 (50)	90	50/50	335 (50)	75	50/50
50	448 (50)	50/50	428 (50)	96	50/50	401 (50)	90	50/50	330 (50)	74	50/50
54	463 (50)	50/50	440 (50)	95	50/50	413 (50)	89	50/50	339 (50)	73	50/50
58	468 (50)	50/50	446 (50)	95	50/50	420 (50)	90	50/50	342 (50)	73	50/50
62	479 (50)	50/50	454 (50)	95	50/50	423 (50)	88	50/50	344 (49)	72	49/50
66	485 (49)	49/50	461 (50)	95	50/50	430 (50)	89	50/50	349 (49)	72	49/50
70	493 (49)	49/50	465 (50)	94	50/50	433 (50)	88	50/50	350 (49)	71	49/50
74	498 (49)	49/50	466 (50)	94	50/50	435 (50)	87	50/50	350 (48)	70	48/50
78	502 (48)	48/50	466 (49)	93	49/50	432 (50)	86	50/50	351 (48)	70	48/50
82	501 (48)	48/50	464 (48)	93	48/50	429 (50)	86	50/50	349 (47)	70	47/50
86	500 (46)	46/50	462 (47)	92	47/50	421 (49)	84	49/50	341 (46)	68	46/50
90	501 (46)	46/50	461 (46)	92	46/50	418 (49)	83	49/50	338 (45)	67	45/50
94	496 (44)	44/50	460 (46)	93	46/50	416 (47)	84	47/50	344 (42)	69	42/50
98	482 (44)	44/50	454 (44)	94	44/50	407 (47)	84	47/50	335 (40)	70	40/50
102	473 (39)	39/50	454 (41)	96	41/50	407 (46)	86	46/50	331 (40)	70	40/50
104	468 (37)	37/50	452 (39)	97	39/50	397 (44)	85	44/50	330 (39)	71	39/50

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

TABLE 3 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE RATS 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	101 (50)	50/50	101 (50)	100	50/50	101 (50)	100	50/50	101 (50)	100	50/50
1	118 (50)	50/50	116 (50)	98	50/50	112 (50)	95	50/50	105 (50)	89	50/50
2	131 (50)	50/50	129 (50)	98	50/50	124 (50)	95	50/50	115 (50)	88	50/50
3	141 (50)	50/50	139 (50)	99	50/50	134 (50)	95	50/50	124 (50)	88	50/50
4	150 (50)	50/50	148 (50)	99	50/50	143 (50)	95	50/50	132 (50)	88	50/50
5	158 (50)	50/50	155 (50)	98	50/50	150 (50)	95	50/50	136 (50)	86	50/50
6	163 (50)	50/50	160 (50)	98	50/50	155 (50)	95	50/50	140 (50)	86	50/50
7	169 (50)	50/50	165 (50)	98	50/50	159 (50)	94	50/50	144 (50)	85	50/50
8	172 (50)	50/50	168 (50)	98	50/50	162 (50)	94	50/50	146 (50)	85	50/50
9	176 (50)	50/50	172 (50)	98	50/50	165 (50)	94	50/50	149 (50)	85	50/50
10	181 (50)	50/50	176 (50)	97	50/50	168 (50)	93	50/50	150 (50)	83	50/50
11	185 (50)	50/50	179 (50)	97	50/50	171 (50)	92	50/50	153 (50)	83	50/50
12	189 (50)	50/50	181 (50)	96	50/50	172 (50)	91	50/50	153 (50)	81	50/50
13	191 (50)	50/50	183 (50)	96	50/50	174 (50)	91	50/50	158 (50)	83	50/50
14	193 (50)	50/50	185 (50)	96	50/50	176 (50)	91	50/50	158 (50)	82	50/50
18	201 (50)	50/50	192 (50)	96	50/50	180 (50)	90	50/50	161 (50)	80	50/50
22	207 (50)	50/50	197 (50)	95	50/50	182 (50)	88	50/50	162 (50)	78	50/50
26	214 (50)	50/50	203 (50)	95	50/50	189 (50)	88	50/50	166 (50)	78	50/50
30	219 (50)	50/50	206 (50)	94	50/50	186 (50)	85	50/50	167 (50)	76	50/50
34	228 (50)	50/50	214 (50)	94	50/50	191 (50)	84	50/50	170 (50)	75	50/50
38	234 (50)	50/50	216 (50)	92	50/50	190 (50)	81	50/50	169 (50)	72	50/50
42	242 (50)	50/50	225 (50)	93	50/50	195 (50)	81	50/50	172 (50)	71	50/50
46	248 (50)	50/50	227 (50)	92	50/50	193 (50)	78	50/50	172 (50)	69	50/50
50	254 (49)	49/50	230 (49)	91	49/50	195 (50)	77	50/50	171 (50)	67	50/50
54	261 (49)	49/50	235 (49)	90	49/50	193 (50)	74	50/50	168 (50)	64	50/50
58	269 (49)	49/50	242 (49)	90	49/50	198 (50)	74	50/50	173 (49)	64	49/50
62	278 (49)	49/50	246 (49)	88	49/50	196 (50)	71	50/50	170 (48)	61	48/50
66	287 (49)	49/50	255 (49)	89	49/50	203 (50)	71	50/50	171 (46)	60	46/50
70	296 (49)	49/50	263 (49)	89	49/50	205 (50)	69	50/50	177 (46)	60	46/50
74	301 (49)	49/50	268 (48)	89	48/50	206 (50)	68	50/50	172 (45)	57	45/50
78	308 (48)	48/50	275 (48)	89	48/50	211 (49)	69	49/50	177 (42)	57	42/50
82	308 (47)	47/50	279 (48)	91	48/50	213 (49)	69	49/50	176 (40)	57	40/50
86	307 (46)	46/50	280 (47)	91	47/50	213 (48)	69	48/50	174 (39)	57	39/50
90	315 (44)	44/50	285 (46)	90	46/50	216 (48)	69	48/50	176 (39)	56	39/50
94	316 (44)	44/50	283 (46)	90	46/50	220 (47)	70	47/50	177 (37)	56	37/50
98	322 (42)	42/50	287 (44)	89	44/50	219 (47)	68	47/50	177 (34)	55	34/50
102	327 (41)	41/50	292 (40)	89	40/50	223 (46)	68	46/50	179 (31)	55	31/50
104	322 (40)	40/50	286 (39)	89	39/50	219 (44)	68	44/50	181 (29)	56	29/50

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

TABLE 4 INCIDENCE OF EXTERNAL AND INTERNAL MASS IN CLINICAL OBSERVATION OF MALE RATS 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	1/50	1/50	2/49	6/48	14/46	15/50(3/13)
	20ppm	0/50	0/50	1/50	1/50	2/50	2/50	8/49	12/46	12/50(3/11)
	40ppm	0/50	0/50	0/50	0/50	1/50	2/50	3/50	7/47	9/50(2/ 6)
	80ppm	0/50	0/50	0/50	0/50	0/50	4/49	6/48	8/43	11/50(2/11)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/50	0/49	0/48	3/46	3/50(2/13)
	20ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/49	1/46	1/50(1/11)
	40ppm	0/50	0/50	0/50	0/50	0/50	0/50	1/50	2/47	2/50(1/ 6)
	80ppm	0/50	0/50	0/50	0/50	0/50	1/49	0/48	1/43	2/50(1/11)

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 RATS 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	0/49	2/49	9/48	12/44	14/50(5/10)
	20ppm	0/50	0/50	0/50	0/50	1/49	1/49	2/48	8/46	8/50(1/11)
	40ppm	0/50	0/50	0/50	0/50	0/50	0/50	3/49	2/47	4/50(2/ 6)
	80ppm	0/50	0/50	0/50	0/50	0/50	2/46	1/42	3/38	4/50(2/21)
Internal mass										
	Control	0/50	0/50	0/50	0/50	0/49	1/49	0/48	1/44	2/50(1/10)
	20ppm	0/50	0/50	0/50	0/50	0/49	0/49	0/48	1/46	1/50(1/11)
	40ppm	0/50	0/50	0/50	0/50	0/50	0/50	0/49	1/47	1/50(1/ 6)
	80ppm	0/50	0/50	0/50	0/50	0/50	0/46	0/42	1/38	1/50(1/21)

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 RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Week on Study	Control		20ppm			40ppm			80ppm		
	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	17.8 (50)	50/50	15.2 (50)	85	50/50	13.5 (50)	76	50/50	13.1 (50)	74	50/50
2	19.1 (50)	50/50	15.1 (50)	79	50/50	14.0 (50)	73	50/50	13.3 (50)	70	50/50
3	20.0 (49)	50/50	15.4 (50)	77	50/50	14.2 (50)	71	50/50	13.0 (50)	65	50/50
4	20.1 (50)	50/50	15.1 (49)	75	50/50	14.0 (50)	70	50/50	12.6 (50)	63	50/50
5	19.5 (50)	50/50	15.0 (50)	77	50/50	13.8 (50)	71	50/50	12.0 (50)	62	50/50
6	18.5 (50)	50/50	14.3 (50)	77	50/50	12.9 (50)	70	50/50	11.1 (50)	60	50/50
7	18.4 (50)	50/50	14.9 (49)	81	50/50	13.3 (50)	72	50/50	11.7 (50)	64	50/50
8	17.8 (50)	50/50	14.7 (50)	83	50/50	13.4 (50)	75	50/50	11.5 (50)	65	50/50
9	18.2 (50)	50/50	14.8 (50)	81	50/50	13.4 (50)	74	50/50	11.6 (50)	64	50/50
10	17.7 (50)	50/50	14.5 (50)	82	50/50	13.1 (50)	74	50/50	11.6 (50)	66	50/50
11	18.2 (50)	50/50	14.9 (50)	82	50/50	13.2 (50)	73	50/50	11.5 (50)	63	50/50
12	18.5 (50)	50/50	14.7 (50)	79	50/50	13.3 (50)	72	50/50	11.4 (50)	62	50/50
13	18.2 (50)	50/50	14.4 (50)	79	50/50	13.0 (50)	71	50/50	11.4 (50)	63	50/50
14	17.3 (50)	50/50	14.2 (50)	82	50/50	12.7 (50)	73	50/50	11.5 (50)	66	50/50
18	18.5 (50)	50/50	15.3 (50)	83	50/50	13.8 (50)	75	50/50	11.7 (50)	63	50/50
22	18.1 (50)	50/50	15.5 (50)	86	50/50	13.4 (50)	74	50/50	12.1 (50)	67	50/50
26	18.3 (50)	50/50	15.2 (50)	83	50/50	13.9 (50)	76	50/50	12.4 (50)	68	50/50
30	18.0 (50)	50/50	15.0 (50)	83	50/50	13.4 (50)	74	50/50	12.4 (50)	69	50/50
34	18.1 (50)	50/50	15.9 (50)	88	50/50	14.3 (50)	79	50/50	13.1 (50)	72	50/50
38	18.7 (50)	50/50	15.9 (50)	85	50/50	14.5 (50)	78	50/50	13.5 (50)	72	50/50
42	19.2 (50)	50/50	17.6 (50)	92	50/50	15.5 (50)	81	50/50	14.4 (50)	75	50/50
46	19.1 (50)	50/50	16.1 (49)	84	50/50	14.9 (50)	78	50/50	14.0 (50)	73	50/50
50	18.4 (50)	50/50	17.0 (50)	92	50/50	15.3 (50)	83	50/50	14.8 (50)	80	50/50
54	19.3 (50)	50/50	16.8 (49)	87	50/50	15.7 (50)	81	50/50	15.5 (50)	80	50/50
58	19.2 (50)	50/50	17.1 (50)	89	50/50	16.5 (50)	86	50/50	16.1 (50)	84	50/50
62	20.3 (50)	50/50	16.8 (50)	83	50/50	15.2 (50)	75	50/50	14.7 (49)	72	49/50
66	20.1 (49)	49/50	18.8 (50)	94	50/50	16.6 (50)	83	50/50	15.6 (49)	78	49/50
70	20.4 (49)	49/50	18.0 (50)	88	50/50	16.4 (50)	80	50/50	15.6 (49)	76	49/50
74	20.7 (48)	49/50	18.2 (50)	88	50/50	16.6 (50)	80	50/50	15.2 (48)	73	48/50
78	20.6 (48)	48/50	17.8 (49)	86	49/50	16.2 (50)	79	50/50	15.2 (48)	74	48/50
82	21.8 (47)	48/50	18.9 (48)	87	48/50	16.4 (50)	75	50/50	15.4 (47)	71	47/50
86	21.8 (46)	46/50	17.5 (46)	80	47/50	15.9 (49)	73	49/50	14.8 (46)	68	46/50
90	22.4 (46)	46/50	18.3 (45)	82	46/50	16.7 (49)	75	49/50	15.3 (45)	68	45/50
94	23.4 (44)	44/50	19.3 (44)	82	46/50	17.0 (47)	73	47/50	15.4 (42)	66	42/50
98	23.6 (44)	44/50	19.5 (44)	83	44/50	17.2 (47)	73	47/50	15.7 (40)	67	40/50
102	25.6 (38)	39/50	20.8 (41)	81	41/50	17.3 (46)	68	46/50	15.4 (40)	60	40/50
104	26.8 (35)	37/50	22.1 (39)	82	39/50	18.6 (44)	69	44/50	16.0 (39)	60	39/50

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

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

Week on Study	Control		20ppm			40ppm			80ppm		
	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	16.7 (50)	50/50	14.1 (50)	84	50/50	11.7 (50)	70	50/50	10.8 (50)	65	50/50
2	16.7 (50)	50/50	12.4 (50)	74	50/50	10.8 (50)	65	50/50	9.8 (50)	59	50/50
3	16.9 (48)	50/50	12.0 (50)	71	50/50	10.5 (50)	62	50/50	9.5 (50)	56	50/50
4	17.7 (45)	50/50	13.0 (50)	73	50/50	10.7 (50)	60	50/50	9.6 (50)	54	50/50
5	19.2 (46)	50/50	12.7 (50)	66	50/50	10.4 (50)	54	50/50	8.9 (50)	46	50/50
6	18.5 (45)	50/50	12.2 (50)	66	50/50	10.1 (50)	55	50/50	8.7 (50)	47	50/50
7	18.8 (46)	50/50	12.5 (50)	66	50/50	9.7 (50)	52	50/50	8.4 (50)	45	50/50
8	18.2 (44)	50/50	11.6 (50)	64	50/50	9.3 (50)	51	50/50	8.1 (50)	45	50/50
9	16.6 (46)	50/50	11.0 (50)	66	50/50	8.8 (50)	53	50/50	8.1 (50)	49	50/50
10	17.1 (45)	50/50	11.5 (50)	67	50/50	8.9 (50)	52	50/50	8.1 (50)	47	50/50
11	18.2 (46)	50/50	11.7 (50)	64	50/50	9.1 (50)	50	50/50	8.0 (50)	44	50/50
12	19.2 (42)	50/50	12.1 (50)	63	50/50	9.2 (50)	48	50/50	8.1 (50)	42	50/50
13	19.3 (46)	50/50	11.0 (50)	57	50/50	9.0 (49)	47	50/50	8.9 (50)	46	50/50
14	19.1 (47)	50/50	11.7 (50)	61	50/50	10.0 (50)	52	50/50	8.2 (50)	43	50/50
18	19.4 (45)	50/50	11.3 (50)	58	50/50	9.1 (50)	47	50/50	8.4 (50)	43	50/50
22	20.0 (46)	50/50	12.0 (50)	60	50/50	9.8 (50)	49	50/50	9.0 (50)	45	50/50
26	19.0 (48)	50/50	11.8 (50)	62	50/50	10.1 (50)	53	50/50	8.5 (50)	45	50/50
30	19.9 (49)	50/50	11.2 (50)	56	50/50	9.6 (50)	48	50/50	9.2 (50)	46	50/50
34	17.9 (43)	50/50	12.2 (50)	68	50/50	10.1 (50)	56	50/50	9.0 (50)	50	50/50
38	18.8 (48)	50/50	11.5 (50)	61	50/50	9.9 (50)	53	50/50	8.8 (50)	47	50/50
42	20.6 (50)	50/50	13.3 (50)	65	50/50	11.4 (50)	55	50/50	10.1 (50)	49	50/50
46	18.3 (49)	50/50	12.0 (50)	66	50/50	10.3 (50)	56	50/50	9.9 (50)	54	50/50
50	17.5 (48)	49/50	14.0 (49)	80	49/50	12.3 (50)	70	50/50	10.4 (50)	59	50/50
54	17.7 (49)	49/50	12.5 (49)	71	49/50	10.5 (50)	59	50/50	10.0 (50)	56	50/50
58	16.6 (49)	49/50	13.6 (49)	82	49/50	11.7 (50)	70	50/50	11.0 (49)	66	49/50
62	17.0 (49)	49/50	12.6 (49)	74	49/50	11.0 (50)	65	50/50	10.7 (48)	63	48/50
66	15.8 (49)	49/50	14.4 (49)	91	49/50	12.7 (50)	80	50/50	10.9 (46)	69	46/50
70	16.4 (49)	49/50	13.4 (49)	82	49/50	11.7 (50)	71	50/50	12.7 (46)	77	46/50
74	16.2 (49)	49/50	14.0 (47)	86	48/50	11.9 (50)	73	50/50	11.3 (45)	70	45/50
78	17.2 (48)	48/50	14.3 (48)	83	48/50	12.8 (49)	74	49/50	13.4 (42)	78	42/50
82	17.3 (47)	47/50	15.0 (48)	87	48/50	13.4 (49)	77	49/50	14.5 (40)	84	40/50
86	18.4 (46)	46/50	14.9 (47)	81	47/50	13.8 (48)	75	48/50	13.8 (39)	75	39/50
90	17.8 (43)	44/50	15.6 (46)	88	46/50	14.7 (48)	83	48/50	15.4 (39)	87	39/50
94	16.9 (43)	44/50	15.4 (46)	91	46/50	14.2 (47)	84	47/50	15.0 (37)	89	37/50
98	18.9 (42)	42/50	15.9 (44)	84	44/50	15.7 (47)	83	47/50	16.1 (34)	85	34/50
102	19.1 (41)	41/50	16.2 (40)	85	40/50	17.1 (46)	90	46/50	16.4 (31)	86	31/50
104	19.0 (40)	40/50	17.0 (39)	89	39/50	17.1 (44)	90	44/50	18.2 (29)	96	29/50

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

TABLE 8 FOOD CONSUMPTION CHANGES OF MALE RATS 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	13.8 (50)	50/50	13.0 (50)	94	50/50	12.4 (50)	90	50/50	11.9 (50)	86	50/50
2	15.1 (50)	50/50	14.3 (50)	95	50/50	13.9 (50)	92	50/50	13.4 (50)	89	50/50
3	15.3 (50)	50/50	14.4 (50)	94	50/50	13.9 (50)	91	50/50	13.3 (50)	87	50/50
4	15.1 (50)	50/50	14.3 (50)	95	50/50	13.7 (50)	91	50/50	12.9 (50)	85	50/50
5	15.0 (50)	50/50	14.5 (50)	97	50/50	14.2 (50)	95	50/50	13.1 (50)	87	50/50
6	14.1 (50)	50/50	13.6 (50)	96	50/50	13.1 (50)	93	50/50	12.1 (50)	86	50/50
7	14.7 (50)	50/50	14.0 (50)	95	50/50	13.4 (50)	91	50/50	12.2 (50)	83	50/50
8	14.6 (50)	50/50	14.5 (50)	99	50/50	13.8 (50)	95	50/50	12.7 (50)	87	50/50
9	14.7 (50)	50/50	14.6 (50)	99	50/50	13.9 (50)	95	50/50	13.0 (50)	88	50/50
10	14.6 (50)	50/50	14.5 (50)	99	50/50	13.8 (50)	95	50/50	13.0 (50)	89	50/50
11	15.1 (50)	50/50	14.8 (50)	98	50/50	14.1 (50)	93	50/50	13.1 (50)	87	50/50
12	14.6 (50)	50/50	14.3 (50)	98	50/50	13.7 (50)	94	50/50	12.8 (50)	88	50/50
13	14.5 (50)	50/50	14.2 (50)	98	50/50	13.7 (50)	94	50/50	13.1 (50)	90	50/50
14	14.5 (50)	50/50	14.1 (50)	97	50/50	13.6 (50)	94	50/50	13.0 (50)	90	50/50
18	15.7 (50)	50/50	15.1 (50)	96	50/50	14.6 (50)	93	50/50	13.7 (50)	87	50/50
22	15.4 (50)	50/50	14.8 (50)	96	50/50	14.1 (50)	92	50/50	13.1 (50)	85	50/50
26	15.5 (50)	50/50	15.0 (50)	97	50/50	14.4 (50)	93	50/50	13.7 (50)	88	50/50
30	15.9 (50)	50/50	15.2 (50)	96	50/50	14.4 (50)	91	50/50	13.6 (50)	86	50/50
34	16.2 (50)	50/50	15.9 (50)	98	50/50	15.1 (50)	93	50/50	13.9 (50)	86	50/50
38	16.7 (50)	50/50	16.2 (50)	97	50/50	15.6 (50)	93	50/50	14.3 (50)	86	50/50
42	16.7 (50)	50/50	16.4 (50)	98	50/50	15.8 (50)	95	50/50	14.5 (50)	87	50/50
46	16.8 (50)	50/50	15.8 (50)	94	50/50	15.5 (50)	92	50/50	14.1 (50)	84	50/50
50	16.6 (50)	50/50	16.4 (50)	99	50/50	15.3 (50)	92	50/50	14.2 (50)	86	50/50
54	16.6 (50)	50/50	15.7 (50)	95	50/50	15.2 (50)	92	50/50	14.0 (50)	84	50/50
58	17.0 (50)	50/50	16.7 (50)	98	50/50	16.3 (50)	96	50/50	14.9 (50)	88	50/50
62	17.7 (49)	50/50	16.7 (50)	94	50/50	15.7 (50)	89	50/50	14.6 (49)	82	49/50
66	17.3 (49)	49/50	17.1 (50)	99	50/50	16.3 (50)	94	50/50	15.0 (49)	87	49/50
70	17.6 (49)	49/50	16.9 (50)	96	50/50	16.1 (50)	91	50/50	15.0 (49)	85	49/50
74	17.6 (49)	49/50	16.7 (50)	95	50/50	15.8 (50)	90	50/50	14.8 (48)	84	48/50
78	17.3 (48)	48/50	16.3 (49)	94	49/50	15.5 (50)	90	50/50	14.7 (48)	85	48/50
82	17.4 (48)	48/50	16.4 (48)	94	48/50	15.2 (50)	87	50/50	14.5 (47)	83	47/50
86	17.3 (46)	46/50	16.2 (47)	94	47/50	15.1 (49)	87	49/50	14.4 (46)	83	46/50
90	16.8 (45)	46/50	16.0 (46)	95	46/50	14.8 (49)	88	49/50	14.2 (45)	85	45/50
94	16.9 (44)	44/50	16.3 (46)	96	46/50	15.1 (47)	89	47/50	14.9 (42)	88	42/50
98	16.0 (43)	44/50	15.6 (44)	98	44/50	14.6 (47)	91	47/50	14.0 (40)	88	40/50
102	16.1 (38)	39/50	16.0 (40)	99	41/50	15.1 (46)	94	46/50	14.0 (39)	87	40/50
104	15.5 (36)	37/50	15.7 (39)	101	39/50	14.5 (44)	94	44/50	13.8 (39)	89	39/50

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

TABLE 9 FOOD CONSUMPTION CHANGES OF FEMALE RATS 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. <49>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.	Av.FC.	% of cont. <50>	No. of Surviv.
1	11.0 (50)	50/50	10.5 (50)	95	50/50	9.6 (50)	87	50/50	8.7 (50)	79	50/50
2	11.1 (50)	50/50	10.7 (50)	96	50/50	10.1 (50)	91	50/50	9.6 (50)	86	50/50
3	11.1 (50)	50/50	10.3 (50)	93	50/50	9.8 (50)	88	50/50	9.2 (50)	83	50/50
4	11.1 (50)	50/50	10.6 (50)	95	50/50	10.0 (50)	90	50/50	9.1 (50)	82	50/50
5	11.1 (50)	50/50	10.7 (50)	96	50/50	10.0 (50)	90	50/50	9.1 (50)	82	50/50
6	10.7 (50)	50/50	9.9 (50)	93	50/50	9.6 (50)	90	50/50	8.7 (50)	81	50/50
7	10.8 (50)	50/50	10.0 (50)	93	50/50	9.5 (50)	88	50/50	8.7 (50)	81	50/50
8	10.4 (50)	50/50	9.9 (50)	95	50/50	9.3 (50)	89	50/50	8.8 (50)	85	50/50
9	10.6 (50)	50/50	9.9 (50)	93	50/50	9.3 (50)	88	50/50	8.8 (50)	83	50/50
10	10.6 (50)	50/50	9.9 (50)	93	50/50	9.2 (50)	87	50/50	8.5 (50)	80	50/50
11	10.7 (50)	50/50	9.8 (50)	92	50/50	9.2 (50)	86	50/50	8.6 (50)	80	50/50
12	10.8 (50)	50/50	9.7 (50)	90	50/50	9.2 (50)	85	50/50	8.5 (50)	79	50/50
13	10.8 (50)	50/50	9.7 (50)	90	50/50	9.2 (50)	85	50/50	8.9 (50)	82	50/50
14	10.5 (50)	50/50	9.9 (50)	94	50/50	9.3 (50)	89	50/50	8.8 (50)	84	50/50
18	10.7 (50)	50/50	9.8 (50)	92	50/50	9.2 (50)	86	50/50	8.7 (50)	81	50/50
22	10.6 (50)	50/50	9.9 (50)	93	50/50	9.3 (50)	88	50/50	8.8 (50)	83	50/50
26	11.3 (50)	50/50	10.5 (50)	93	50/50	9.7 (50)	86	50/50	9.0 (50)	80	50/50
30	11.0 (50)	50/50	10.0 (50)	91	50/50	9.2 (50)	84	50/50	8.7 (50)	79	50/50
34	11.8 (50)	50/50	10.9 (50)	92	50/50	9.6 (50)	81	50/50	8.9 (50)	75	50/50
38	11.7 (50)	50/50	10.6 (50)	91	50/50	9.5 (50)	81	50/50	8.8 (50)	75	50/50
42	12.0 (50)	50/50	11.3 (50)	94	50/50	10.0 (50)	83	50/50	9.0 (50)	75	50/50
46	11.6 (50)	50/50	10.7 (50)	92	50/50	9.4 (50)	81	50/50	8.9 (50)	77	50/50
50	11.9 (49)	49/50	11.2 (49)	94	49/50	10.1 (50)	85	50/50	9.1 (50)	76	50/50
54	11.7 (49)	49/50	10.7 (49)	91	49/50	9.4 (50)	80	50/50	8.6 (50)	74	50/50
58	12.2 (49)	49/50	11.6 (49)	95	49/50	10.2 (50)	84	50/50	9.5 (49)	78	49/50
62	12.5 (49)	49/50	11.1 (49)	89	49/50	9.7 (50)	78	50/50	9.2 (48)	74	48/50
66	12.0 (49)	49/50	12.1 (49)	101	49/50	10.6 (50)	88	50/50	9.4 (46)	78	46/50
70	12.5 (49)	49/50	12.0 (49)	96	49/50	10.6 (50)	85	50/50	10.4 (46)	83	46/50
74	12.3 (49)	49/50	11.9 (48)	97	48/50	10.6 (50)	86	50/50	9.6 (45)	78	45/50
78	12.6 (48)	48/50	12.1 (48)	96	48/50	10.8 (49)	86	49/50	10.2 (42)	81	42/50
82	12.4 (47)	47/50	11.9 (48)	96	48/50	10.7 (49)	86	49/50	10.3 (40)	83	40/50
86	12.4 (46)	46/50	11.9 (47)	96	47/50	10.6 (48)	85	48/50	10.3 (39)	83	39/50
90	13.0 (44)	44/50	12.5 (46)	96	46/50	11.0 (48)	85	48/50	10.8 (39)	83	39/50
94	12.7 (44)	44/50	11.9 (46)	94	46/50	11.0 (47)	87	47/50	10.6 (37)	83	37/50
98	13.0 (42)	42/50	12.1 (44)	93	44/50	10.9 (47)	84	47/50	10.8 (34)	83	34/50
102	13.7 (40)	41/50	12.7 (39)	93	40/50	11.5 (46)	84	46/50	11.0 (31)	80	31/50
104	12.1 (39)	40/50	11.5 (39)	95	39/50	10.7 (44)	88	44/50	11.0 (29)	91	29/50

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

TABLE 10 NEOPLASTIC LESIONS INCIDENCE AND STATISTICAL ANALYSIS OF MALE RAT 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)	0/50(0.0)	0/50(0.0)	0/50(0.0)	3/50(6.0)
Adjusted rates(b)	0.0	0.0	0.0	7.69
Terminal rates(c)	0/37(0.0)	0/39(0.0)	0/44(0.0)	3/39(7.7)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0038**?			
Combined analysis (d)	P=------			
Cochran-Armitage test(e)	P=0.0079**			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.1212
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	0.0	0.0	10.26
Terminal rates(c)	0/37(0.0)	0/39(0.0)	0/44(0.0)	4/39(10.3)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0009**?			
Combined analysis (d)	P=------			
Cochran-Armitage test(e)	P=0.0021**			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.0587

(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 RAT 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)	1/50(2.0)	0/50(0.0)	3/50(6.0)	4/50(8.0)
Adjusted rates(b)	2.50	0.0	6.82	10.81
Terminal rates(c)	1/40(2.5)	0/39(0.0)	3/44(6.8)	2/29(6.9)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0165*			
Combined analysis (d)	P=------			
Cochran-Armitage test(e)	P=0.0510			
Fisher Exact test(e)		P=0.5000	P=0.3087	P=0.1811
SITE : liver				
TUMOR : hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	0/50(0.0)	0/50(0.0)	0/50(0.0)	4/50(8.0)
Adjusted rates(b)	0.0	0.0	0.0	11.43
Terminal rates(c)	0/40(0.0)	0/39(0.0)	0/44(0.0)	2/29(6.9)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0004**?			
Combined analysis (d)	P=------			
Cochran-Armitage test(e)	P=0.0021**			
Fisher Exact test(e)		P=0.5000	P=0.5000	P=0.0587
SITE : liver				
TUMOR : hepatocellular adenoma, hepatocellular carcinoma				
Tumor rate				
Overall rates(a)	1/50(2.0)	0/50(0.0)	3/50(6.0)	6/50(12.0)
Adjusted rates(b)	2.50	0.0	6.82	16.22
Terminal rates(c)	1/40(2.5)	0/39(0.0)	3/44(6.8)	3/29(10.3)
Statistical analysis				
Peto test				
Standard method(d)	P=------			
Prevalence method(d)	P=0.0015**			
Combined analysis (d)	P=------			
Cochran-Armitage test(e)	P=0.0061**			
Fisher Exact test(e)		P=0.5000	P=0.3087	P=0.0559

(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 RATS WITH SELECTED NON-NEOPLASTIC LESIONS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

Group name <all animal No.>(sacrificed animal No.)		Male Control <50> (37)	Male 20ppm <50> (39)	Male 40ppm <50> (44)	Male 80ppm <50> (39)	Female Control <50> (40)	Female 20ppm <50> (39)	Female 40ppm <50> (44)	Female 80ppm <50> (29)
Liver		7 (7)	12 (12)	20** (20)**	36** (36)**	0 (0)	4 (4)	22** (22)**	26** (24)**
acidophilic cell focus	+	6 (6)	8 (8)	7 (7)	10 (10)	0 (0)	3 (3)	11 (11)	9 (7)
	2+	1 (1)	4 (4)	13 (13)	26 (26)	0 (0)	1 (1)	11 (11)	17 (17)
	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)
Liver		17 (16)	15 (13)	16 (15)	20 (17)	4 (4)	8 (7)	19** (18)**	19** (17)**
basophilic cell focus	+	13 (12)	10 (8)	13 (13)	18 (15)	4 (4)	7 (7)	14 (13)	11 (10)
	2+	4 (4)	5 (5)	3 (2)	2 (2)	0 (0)	1 (0)	5 (5)	8 (7)
	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)
Kidney		0 (0)	1 (1)	5 (5)	11** (9)**	0 (0)	3 (3)	35** (32)**	29** (20)**
infarct	+	0 (0)	1 (1)	5 (5)	11 (9)	0 (0)	2 (2)	15 (13)	21 (14)
	2+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (15)	7 (5)
	3+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	4 (4)	1 (1)
	4+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kidney		0 (0)	0 (0)	1 (1)	20** (16)**	0 (0)	1 (1)	35** (32)**	42** (25)**
papillary necrosis	+	0 (0)	0 (0)	1 (1)	10 (9)	0 (0)	1 (1)	11 (11)	4 (3)
	2+	0 (0)	0 (0)	0 (0)	9 (6)	0 (0)	0 (0)	16 (14)	10 (7)
	3+	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	8 (7)	28 (15)
	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 12 NUMBER OF RATS WITH SELECTED NON-NEOPLASTIC LESIONS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE (Continued)

Group name		Male				Female			
		Control	20ppm	40ppm	80ppm	Control	20ppm	40ppm	80ppm
<all animal No.>(sacrificed animal No.)		<50> (37)	<50> (39)	<50> (44)	<50> (39)	<50> (40)	<50> (39)	<50> (44)	<50> (29)
Kidney		0 (0)	6* (6)*	8** (8)*	29** (24)**	0 (0)	13** (10)**	36** (31)**	47** (28)**
mineralization : papilla	+	0 (0)	6 (6)	8 (8)	28 (24)	0 (0)	13 (10)	32 (27)	33 (18)
	2+	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	3 (3)	14 (10)
	3+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
	4+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kidney		6 (4)	16* (15)*	27** (24)**	28** (21)**	19 (15)	22 (21)	42** (38)**	45** (29)**
urothelial hyperplasia :	+	6 (4)	15 (14)	27 (24)	28 (21)	19 (15)	22 (21)	32 (29)	34 (20)
pelvis	2+	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	9 (8)	11 (9)
	3+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	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 RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

		Male				Female			
Group		Control	20ppm	40ppm	80ppm	Control	20ppm	40ppm	80ppm
Number of dead or moribund animals		13	11	6	11	10	11	6	21
No microscopical confirmation		0	0	0	1	0	0	0	2
Pneumonia		0	0	0	0	1	0	0	0
Urinary system lesion		0	0	0	1	0	0	0	0
Nervous system disorder		0	0	0	1	0	0	0	0
Urinary retention		0	1	0	0	0	0	1	0
Renal lesion		0	0	0	0	0	0	0	15
Chronic nephropathy		0	2	1	0	0	0	0	0
Tumor death	leukemia	3	2	0	1	3	2	0	2
	skin/appendage	0	1	1	0	1	0	0	0
	subcutis	1	2	1	1	1	1	0	1
	lung	0	0	0	1	0	1	0	0
	lymph node	0	1	0	0	0	0	0	0
	spleen	0	0	1	1	0	0	0	0
	pituitary	7	0	2	0	4	5	2	1
	uterus	0	0	0	0	0	2	1	0
	preputial/clitoral gland	1	0	0	0	0	0	1	0
	bone	0	1	0	0	0	0	0	0
	vertebra	0	0	0	1	0	0	0	0
	mediastinum	0	0	0	1	0	0	0	0
	peritoneum	1	1	0	1	0	0	0	0
	retroperitoneum	0	0	0	1	0	0	1	0

FIGURES

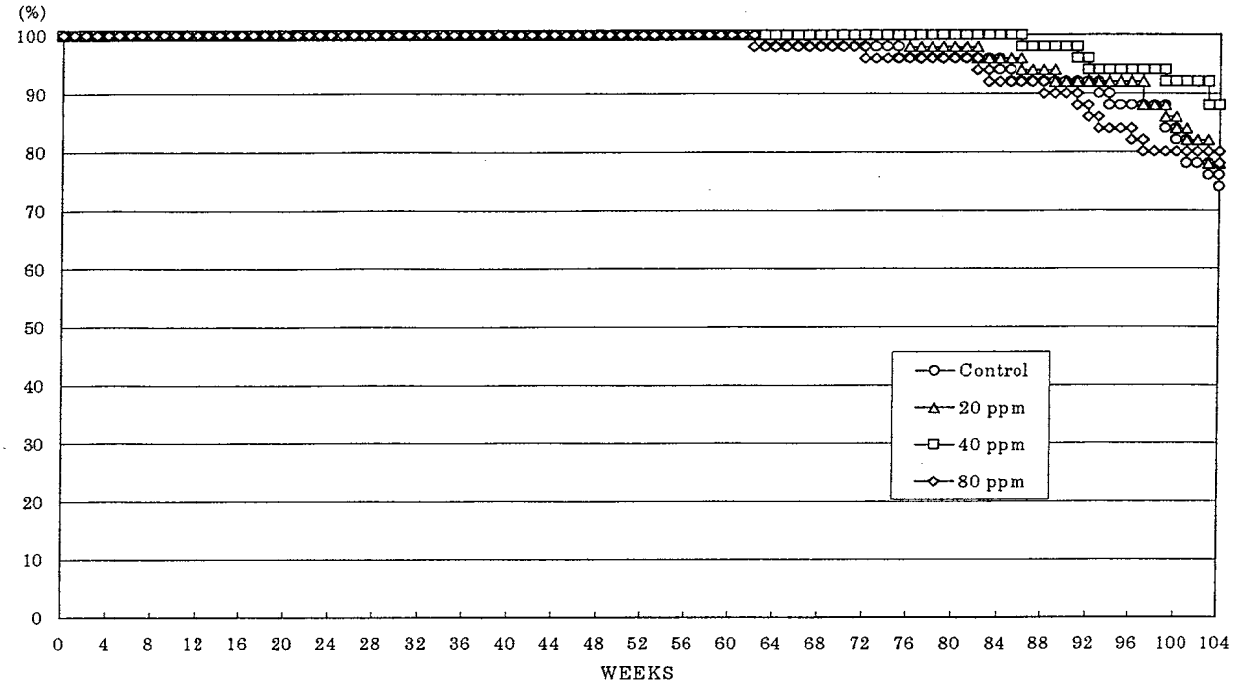


FIGURE 1 SURVIVAL ANIMAL RATE OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

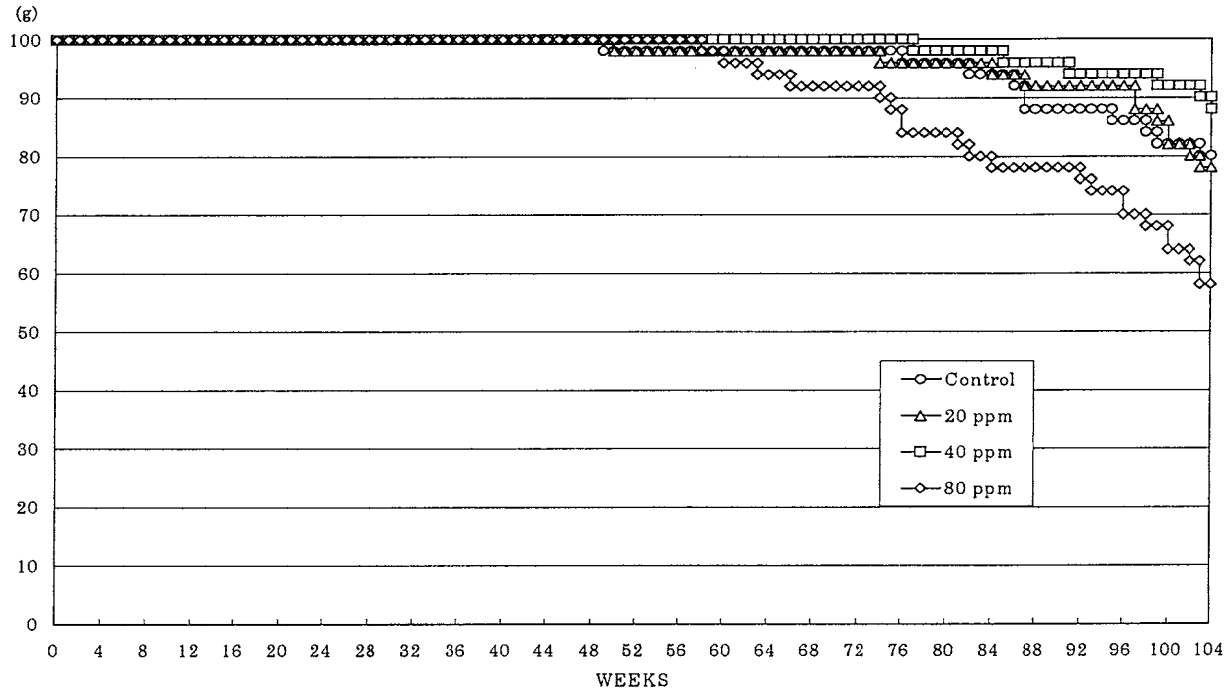


FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

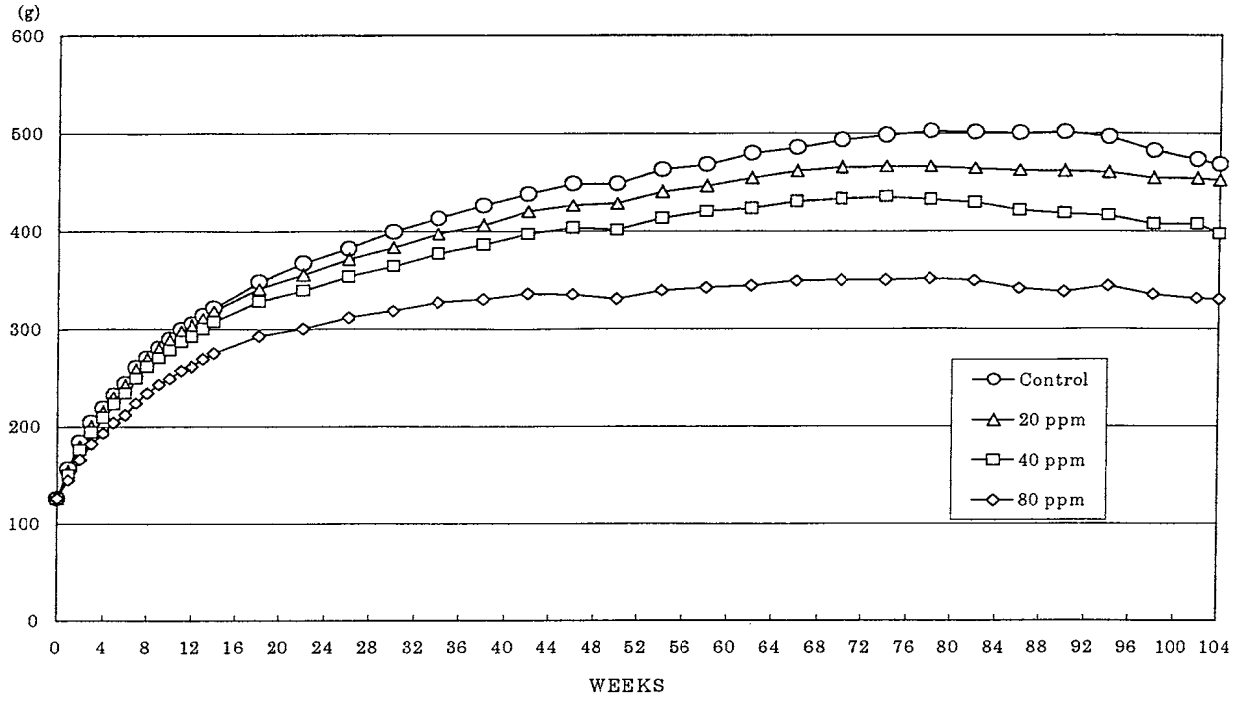


FIGURE 3 BODY WEIGHT CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

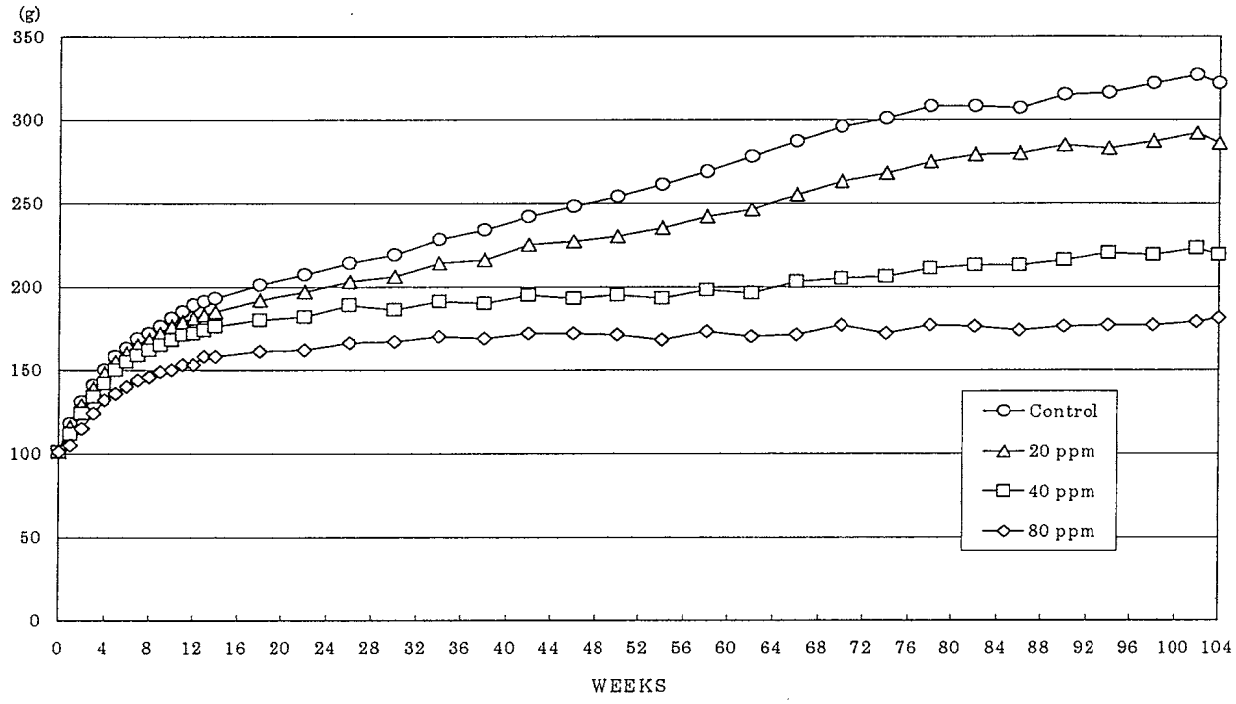


FIGURE 4 BODY WEIGHT CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

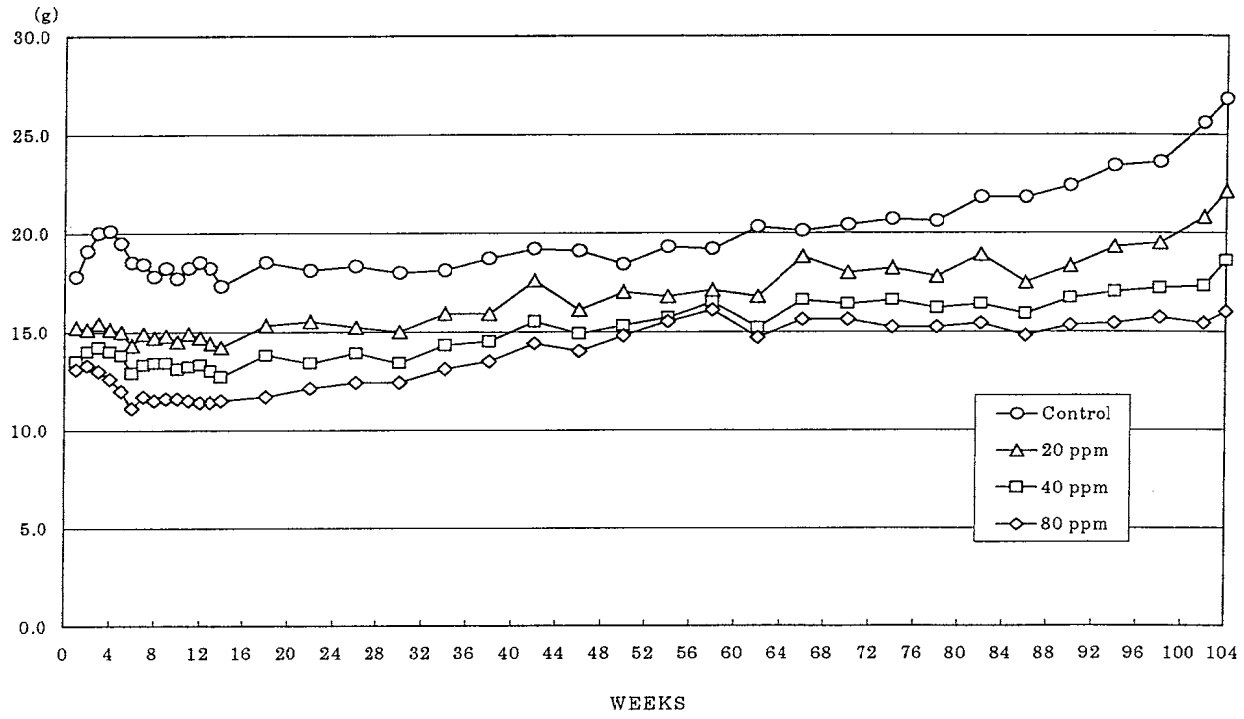


FIGURE 5 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

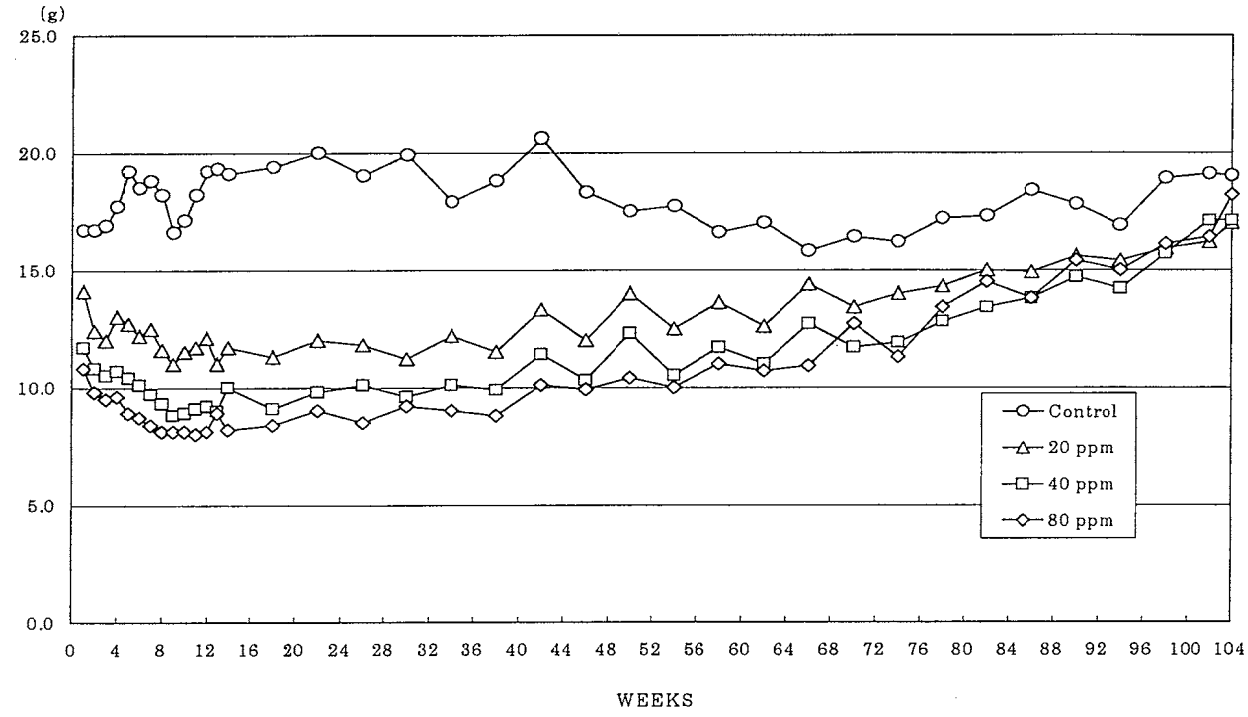


FIGURE 6 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

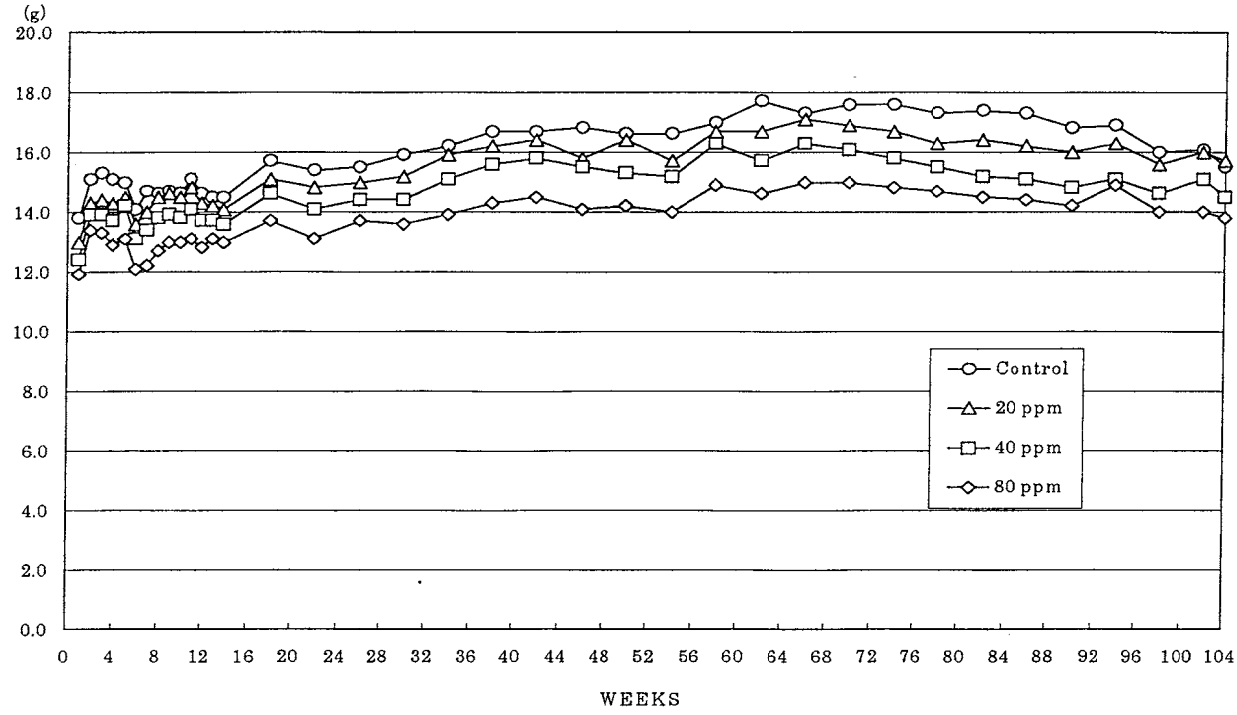


FIGURE 7 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

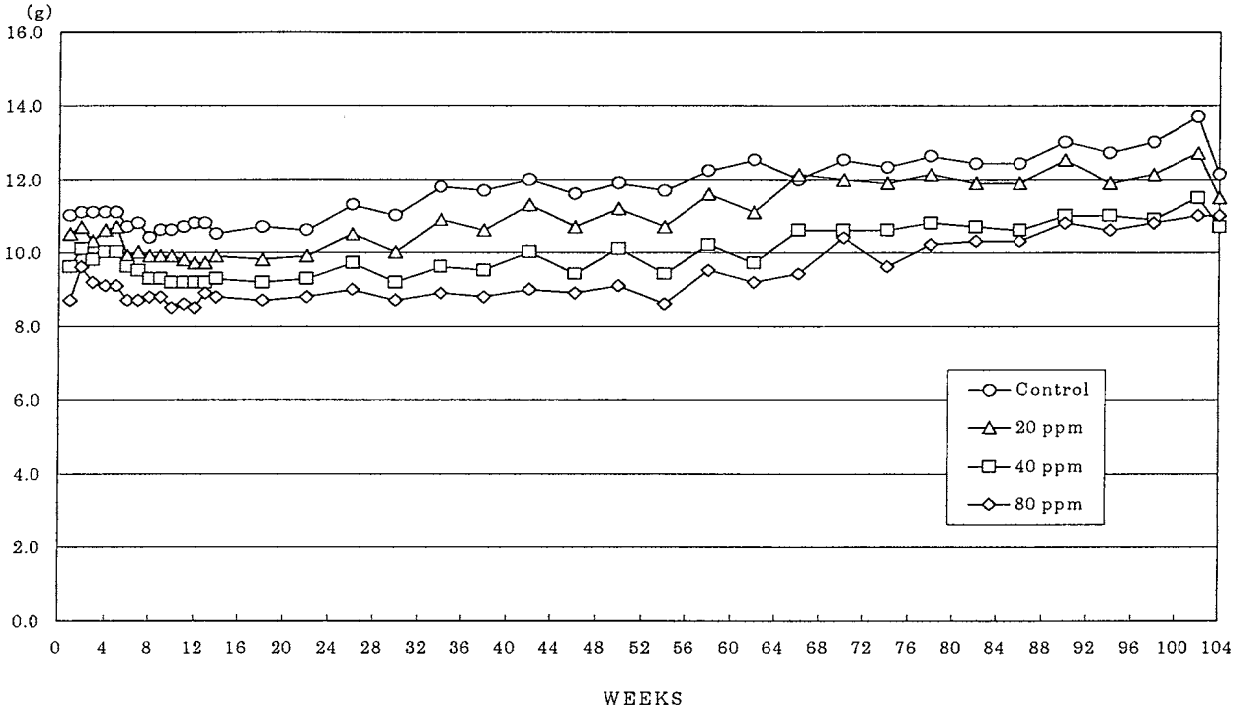


FIGURE 8 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF HYDRAZINE MONOHYDRATE

PHOTOGRAPHS

PHOTOGRAPH 1 LIVER: ACIDOPHILIC CELL FOCUS,
RAT, MALE, 80ppm, ANIMAL NO. 0284-1315 (H&E)

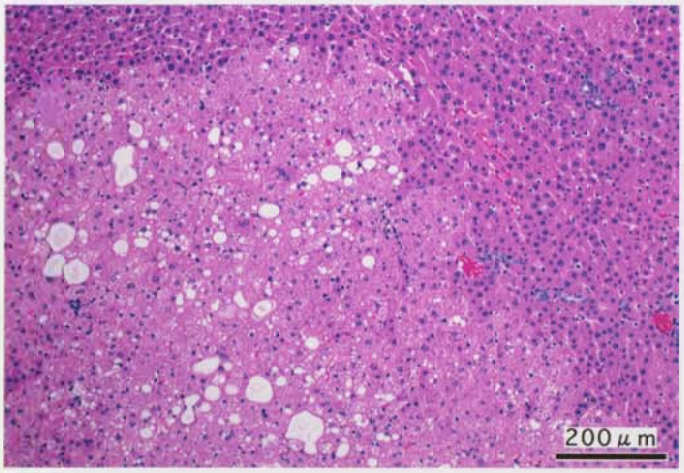
PHOTOGRAPH 2 LIVER: BASOPHILIC CELL FOCUS,
RAT, MALE, 80ppm, ANIMAL NO. 0284-1319 (H&E)

PHOTOGRAPH 3 LIVER: HEPATOCELLULAR ADENOMA,
RAT, FEMALE, 80ppm, ANIMAL NO. 0284-2306 (H&E)

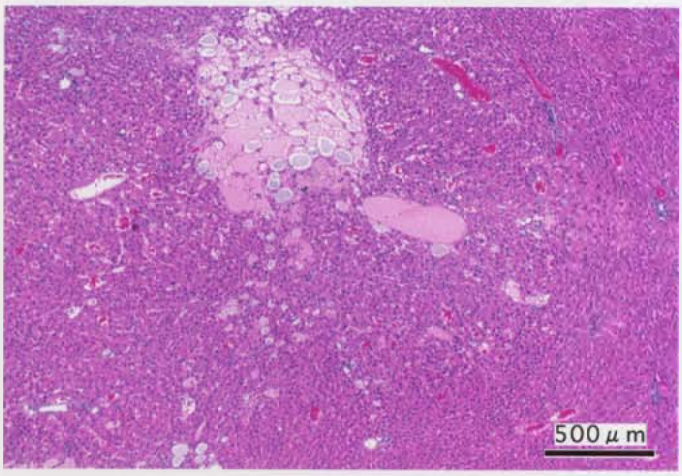
PHOTOGRAPH 4 KIDNEY: HEPATOCELLULAR CARCINOMA,
RAT, FEMALE, 80ppm, ANIMAL NO. 0284-2334 (H&E)

PHOTOGRAPH 5 KIDNEY: INFRACT,
RAT, FEMALE, 80ppm, ANIMAL NO. 0284-2343 (H&E)

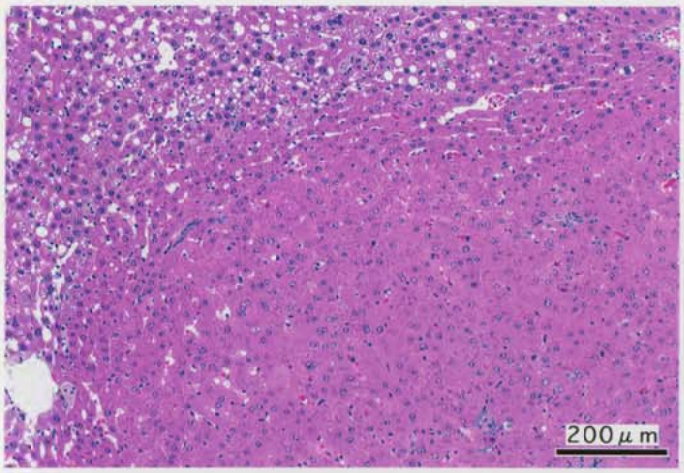
PHOTOGRAPH 6 KIDNEY: (A) PAPILLARY NECROSIS
(B) MINERALIZATION PAPILLA
(C) UROTHELIAL HYPERPLASIA: PELVIS
RAT, FEMALE, 80ppm, ANIMAL NO. 0284-2343(H&E)



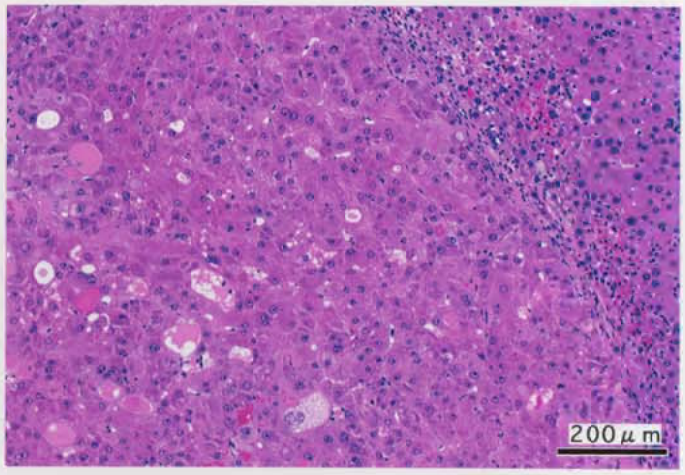
PHOTOGRAPH. 1



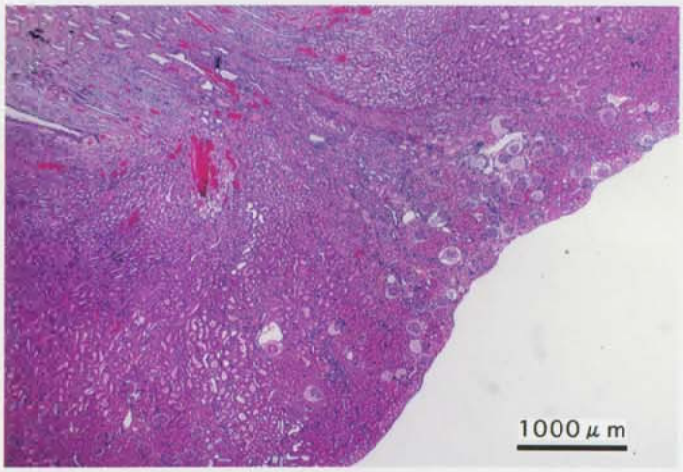
PHOTOGRAPH. 2



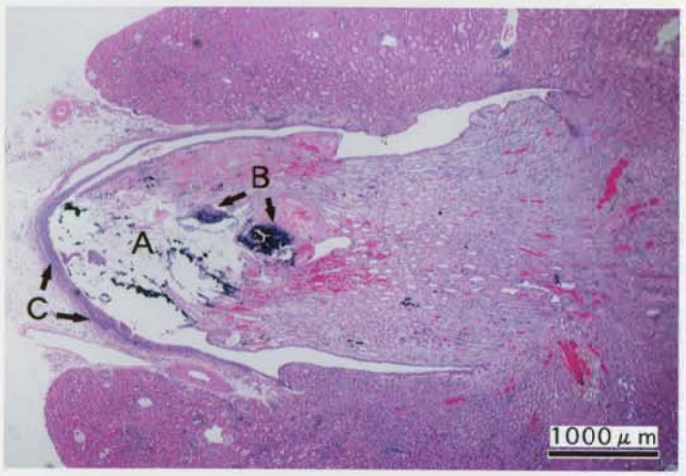
PHOTOGRAPH. 3



PHOTOGRAPH. 4



PHOTOGRAPH. 5



PHOTOGRAPH. 6