Summary of Drinking Water Carcinogenicity Study of Methyl Acetoacetate in BDF1 Mice

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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 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 September 28, 2005.

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

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Purpose, materials and methods

Methyl acetoacetate (MAA, methyl 3-oxobutyrate, CAS No. 105-45-3) is a colorless clear liquid with a melting point of -80°C and a boiling point of 171.7°C, and is soluble in water (38 g/l00 mL water).

The carcinogenicity and chronic toxicity of MAA were examined in groups of 50 Crj:BDF1 mice of both sexes administered MAA in drinking water for 2 years (104 weeks). The drinking water concentration of MAA was 0, 2000, 6325 or 20000 ppm (w/w). The highest dose level was chosen so as not to exceed the maximum tolerated dose (MTD), based on both growth rate and toxicity in the previous 13-week toxicity study. MAA was analyzed for purity and stability by both infrared spectrometry and gas chromatography before and after its use. The concentrations of MAA in drinking water were determined by gas chromatography at the time of preparation, and on the 8th 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. For hematology and blood biochemistry, the surviving animals were bled under ether anesthesia, after they were fasted overnight, at the terminal necropsy. Organs and tissues were removed, weighed and examined for macroscopic lesions at necropsy. The organs and tissues were fixed and embedded in paraffin. Tissue sections of 5 μm thick were prepared and stained with hematoxylin and eosin and examined for histopathology. Incidences of neoplastic lesions were statistically analyzed by Fisher's exact test. A positive trend of dose-response relationship for the neoplastic incidence was analyzed by Peto's test. Incidences of non-neoplastic lesions and urinalysis were analyzed by Chi-square test. Changes in body weight, water consumption, food consumption, hematological and blood biochemical parameters, and organ weights were analyzed by Dunnett's test. The present studies were conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice and with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".

Results

No significant difference in survival rate, body weight or food consumption was found between any MAA-administered group of either sex and the respective control. Water consumption was slightly decreased in the 20000 ppm-administered groups of both sexes as compared with the respective controls.

No significant increase in the incidence of neoplastic lesions or tumor-related lesions was found between any of the MAA-administered groups of either sex and the respective control. No increase in the incidence of non-neoplastic lesions was noted in any MAA-administered group of either sex.

Conclusions

In mice, there was no evidence of carcinogenic activity of MAA in males or females.

TABLES

TABLES (CONTINUED)

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2000 ppm			6325 ppm			20000 ppm		
	Av. Wt.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>
0	23.5 (50)	50 / 50	23.5 (50)	100	50 / 50	23.5 (50)	100	50 / 50	23.5 (50)	100	50 / 50
1	24.8 (50)	50 / 50	24.7 (50)	100	50 / 50	24.5 (50)	99	50 / 50	24.6 (50)	99	50 / 50
2	25.5 (50)	50 / 50	25.5 (50)	100	50 / 50	25.4 (50)	100	50 / 50	25.4 (50)	100	50 / 50
3	26.0 (50)	50 / 50	26.1 (50)	100	50 / 50	25.9 (50)	100	50 / 50	26.1 (50)	100	50 / 50
4	27.0 (50)	50 / 50	27.0 (50)	100	50 / 50	26.7 (50)	99	50 / 50	27.1 (50)	100	50 / 50
5	27.7 (50)	50 / 50	27.8 (50)	100	50 / 50	27.5 (50)	99	50 / 50	27.7 (50)	100	50 / 50
6	28.2 (50)	50 / 50	28.6 (50)	101	50 / 50	28.2 (50)	100	50 / 50	28.5 (50)	101	50 / 50
7	28.9 (50)	50 / 50	29.1 (50)	101	50 / 50	28.5 (50)	99	50 / 50	28.9 (50)	100	50 / 50
8	29.4 (50)	50 / 50	29.8 (50)	101	50 / 50	29.2 (50)	99	50 / 50	29.5 (50)	100	50 / 50
9	30.4 (50)	50 / 50	30.8 (50)	101	50 / 50	29.9 (50)	98	50 / 50	30.3 (50)	100	50 / 50
10	31.0 (50)	50 / 50	31.5 (50)	102	50 / 50	30.7 (50)	99	50 / 50	31.1 (50)	100	50 / 50
11	31.8 (50)	50 / 50	32.2 (50)	101	50 / 50	31.6 (50)	99	50 / 50	31.8 (50)	100	50 / 50
12	32.8 (50)	50 / 50	33.1 (50)	101	50 / 50	32.3 (50)	98	50 / 50	32.7 (50)	100	50 / 50
13	33.2 (50)	50 / 50	33.5 (50)	101	50 / 50	32.9 (50)	99	50 / 50	32.8 (50)	99	50 / 50
14	33.9 (50)	50 / 50	34.6 (50)	102	50 / 50	33.6 (50)	99	50 / 50	33.7 (50)	99	50 / 50
18	35.9 (50)	50 / 50	36.7 (50)	102	50 / 50	35.7 (50)	99	50 / 50	35.7 (50)	99	50 / 50
22	38.3 (50)	50 / 50	39.3 (50)	103	50 / 50	38.2 (50)	100	50 / 50	38.5 (50)	101	50 / 50
26	39.8 (50)	50 / 50	40.8 (50)	103	50 / 50	39.9 (50)	100	50 / 50	39.8 (50)	100	50 / 50
30	41.4 (50)	50 / 50	42.8 (50)	103	50 / 50	41.5 (50)	100	50 / 50	41.3 (50)	100	50 / 50
34	42.2 (50)	50 / 50	43.7 (50)	104	50 / 50	42.5 (50)	101	50 / 50	42.2 (50)	100	50 / 50
38	43.6 (50)	50 / 50	45.2 (50)	104	50 / 50	43.9 (50)	101	50 / 50	43.6 (50)	100	50 / 50
42	44.9 (50)	50 / 50	46.6 (50)	104	50 / 50	45.1 (50)	100	50 / 50	44.9 (50)	100	50 / 50
46	45.7 (50)	50 / 50	47.5 (50)	104	50 / 50	46.3 (50)	101	50 / 50	45.8 (50)	100	50 / 50
50	46.5 (50)	50 / 50	48.5 (50)	104	50 / 50	47.4 (50)	102	50 / 50	46.7 (50)	100	50 / 50
54	47.9 (49)	49 / 50	49.3 (50)	103	50 / 50	48.0 (50)	100	50 / 50	47.9 (50)	100	50 / 50
58	49.3 (48)	48 / 50	50.5 (50)	102	50 / 50	49.0 (50)	99	50 / 50	48.8 (50)	99	50 / 50
62	49.5 (48)	48 / 50	50.8 (50)	103	50 / 50	49.2 (50)	99	50 / 50	49.2 (50)	99	50 / 50
66	50.1 (48)	48 / 50	50.9 (49)	102	49 / 50	49.9 (50)	100	50 / 50	49.7 (50)	99	50 / 50
70	50.2 (48)	48 / 50	50.8 (49)	101	49 / 50	49.7 (50)	99	50 / 50	49.8 (50)	99	50 / 50
74	50.9 (47)	47 / 50	52.3 (47)	103	47 / 50	50.5 (49)	99	49 / 50	49.9 (49)	98	49 / 50
78	52.0 (45)	45 / 50	53.1 (47)	102	47 / 50	51.0 (48)	98	48 / 50	51.3 (48)	99	48 / 50
82	52.1 (43)	43 / 50	53.1 (47)	102	47 / 50	51.7 (46)	99	46 / 50	51.2 (48)	98	48 / 50
86	50.7 (42)	42 / 50	52.9 (46)	104	46 / 50	51.3 (45)	101	45 / 50	51.0 (46)	101	46 / 50
90	50.7 (35)	35 / 50	52.3 (45)	103	45 / 50	51.4 (43)	101	43 / 50	51.4 (44)	101	44 / 50
94	48.9 (35)	35 / 50	51.7 (43)	106	43 / 50	50.3 (42)	103	42 / 50	50.3 (43)	103	43 / 50
98	49.9 (29)	29 / 50	51.7 (41)	104	41 / 50	49.5 (42)	99	42 / 50	50.8 (39)	102	39 / 50
102	50.1 (28)	28 / 50	50.3 (40)	100	40 / 50	48.6 (39)	97	39 / 50	50.1 (38)	100	38 / 50
104	51.4 (25)	25 / 50	50.0 (37)	97	37 / 50	47.2 (37)	92	37 / 50	49.7 (37)	97	37 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. Wt. : Averaged body weight (Unit : g).

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2000 ppm			6325 ppm			20000 ppm		
	Av. Wt.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>	Av. Wt.	% of cont.	No. of Surviv. <50>
0	19.8 (50)	50 / 50	19.8 (50)	100	50 / 50	19.8 (50)	100	50 / 50	19.8 (50)	100	50 / 50
1	20.3 (50)	50 / 50	20.4 (50)	100	50 / 50	20.3 (50)	100	50 / 50	20.1 (50)	99	50 / 50
2	20.4 (50)	50 / 50	20.7 (50)	101	50 / 50	20.7 (50)	101	50 / 50	20.7 (50)	101	50 / 50
3	20.8 (50)	50 / 50	21.0 (50)	101	50 / 50	20.9 (50)	100	50 / 50	20.9 (50)	100	50 / 50
4	21.3 (50)	50 / 50	21.4 (50)	100	50 / 50	21.7 (50)	102	50 / 50	21.6 (50)	101	50 / 50
5	21.9 (50)	50 / 50	21.9 (50)	100	50 / 50	22.0 (50)	100	50 / 50	21.8 (50)	100	50 / 50
6	22.4 (50)	50 / 50	22.9 (50)	102	50 / 50	22.7 (50)	101	50 / 50	22.2 (50)	99	50 / 50
7	22.6 (50)	50 / 50	22.7 (50)	100	50 / 50	22.6 (50)	100	50 / 50	22.5 (50)	100	50 / 50
8	23.0 (50)	50 / 50	23.2 (50)	101	50 / 50	23.0 (50)	100	50 / 50	23.2 (50)	101	50 / 50
9	23.5 (50)	50 / 50	23.7 (50)	101	50 / 50	23.6 (50)	100	50 / 50	23.6 (50)	100	50 / 50
10	24.0 (50)	50 / 50	24.1 (50)	100	50 / 50	24.0 (50)	100	50 / 50	23.8 (50)	99	50 / 50
11	24.1 (50)	50 / 50	24.1 (50)	100	50 / 50	24.3 (50)	101	50 / 50	24.1 (50)	100	50 / 50
12	24.3 (50)	50 / 50	24.7 (50)	102	50 / 50	24.5 (50)	101	50 / 50	24.0 (50)	99	50 / 50
13	24.4 (50)	50 / 50	24.8 (50)	102	50 / 50	24.7 (50)	101	50 / 50	24.3 (50)	100	50 / 50
14	24.8 (50)	50 / 50	24.9 (50)	100	50 / 50	24.9 (50)	100	50 / 50	24.6 (50)	99	50 / 50
18	25.6 (50)	50 / 50	25.7 (50)	100	50 / 50	25.8 (50)	101	50 / 50	25.7 (50)	100	50 / 50
22	27.0 (50)	50 / 50	27.2 (50)	101	50 / 50	27.0 (50)	100	50 / 50	26.5 (50)	98	50 / 50
26	27.3 (50)	50 / 50	27.8 (50)	102	50 / 50	28.1 (50)	103	50 / 50	27.4 (50)	100	50 / 50
30	27.9 (50)	50 / 50	28.7 (50)	103	50 / 50	28.8 (50)	103	50 / 50	28.3 (50)	101	50 / 50
34	28.5 (50)	50 / 50	29.2 (50)	102	50 / 50	29.3 (50)	103	50 / 50	28.6 (50)	100	50 / 50
38	29.2 (50)	50 / 50	30.1 (50)	103	50 / 50	30.2 (49)	103	49 / 50	29.3 (50)	100	50 / 50
42	29.8 (50)	50 / 50	30.8 (50)	103	50 / 50	30.8 (49)	103	49 / 50	30.0 (50)	101	50 / 50
46	30.6 (50)	50 / 50	31.4 (50)	103	50 / 50	32.0 (49)	105	49 / 50	30.5 (50)	100	50 / 50
50	31.2 (50)	50 / 50	32.3 (49)	104	49 / 50	32.5 (49)	104	49 / 50	31.3 (50)	100	50 / 50
54	31.9 (50)	50 / 50	32.9 (49)	103	49 / 50	33.0 (49)	103	49 / 50	31.4 (49)	98	49 / 50
58	32.3 (50)	50 / 50	33.9 (49)	105	49 / 50	33.7 (49)	104	49 / 50	32.1 (49)	99	49 / 50
62	32.8 (48)	48 / 50	33.8 (49)	103	49 / 50	34.7 (49)	106	49 / 50	32.6 (47)	99	47 / 50
66	33.6 (46)	46 / 50	34.4 (49)	102	49 / 50	34.9 (49)	104	49 / 50	33.3 (47)	99	47 / 50
70	33.0 (44)	44 / 50	34.1 (49)	103	49 / 50	34.9 (49)	106	49 / 50	33.4 (47)	101	47 / 50
74	33.6 (43)	43 / 50	34.3 (47)	102	47 / 50	35.1 (49)	104	49 / 50	33.2 (44)	99	44 / 50
78	34.2 (43)	43 / 50	35.4 (47)	104	47 / 50	35.8 (48)	105	48 / 50	33.8 (42)	99	42 / 50
82	34.8 (40)	40 / 50	35.4 (43)	102	43 / 50	35.9 (48)	103	48 / 50	33.7 (40)	97	40 / 50
86	34.7 (39)	39 / 50	35.2 (40)	101	40 / 50	36.1 (47)	104	47 / 50	33.7 (38)	97	38 / 50
90	34.7 (38)	38 / 50	34.5 (35)	99	35 / 50	35.9 (46)	103	46 / 50	33.6 (34)	97	34 / 50
94	34.6 (38)	38 / 50	35.0 (34)	101	34 / 50	36.0 (44)	104	44 / 50	34.1 (32)	99	32 / 50
98	34.4 (37)	37 / 50	34.6 (27)	101	27 / 50	35.9 (41)	104	41 / 50	33.6 (31)	98	31 / 50
102	33.9 (36)	36 / 50	34.5 (25)	102	25 / 50	35.6 (38)	105	38 / 50	32.8 (28)	97	28 / 50
104	33.9 (36)	36 / 50	33.5 (23)	99	23 / 50	35.7 (31)	105	31 / 50	32.3 (26)	95	26 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. Wt. : Averaged body weight (Unit : g).

TABLE 3 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2000 ppm			6325 ppm			20000 ppm		
	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>
1	3.8 (50)	50 / 50	3.7 (50)	97	50 / 50	3.8 (50)	100	50 / 50	3.8 (50)	100	50 / 50
2	3.7 (50)	50 / 50	3.7 (50)	100	50 / 50	4.2 (50)	114	50 / 50	4.2 (50)	114	50 / 50
3	3.7 (50)	50 / 50	3.7 (50)	100	50 / 50	3.7 (50)	100	50 / 50	3.7 (50)	100	50 / 50
4	3.7 (50)	50 / 50	3.7 (50)	100	50 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50
5	3.8 (50)	50 / 50	3.9 (50)	103	50 / 50	3.9 (50)	103	50 / 50	3.8 (50)	100	50 / 50
6	3.8 (50)	50 / 50	3.9 (50)	103	50 / 50	3.9 (50)	103	50 / 50	3.9 (50)	103	50 / 50
7	3.9 (50)	50 / 50	3.9 (50)	100	50 / 50	3.9 (50)	100	50 / 50	3.9 (50)	100	50 / 50
8	3.9 (50)	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50
9	3.9 (50)	50 / 50	3.9 (50)	100	50 / 50	3.9 (50)	100	50 / 50	3.8 (50)	97	50 / 50
10	3.9 (50)	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50
11	3.9 (50)	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50
12	4.0 (50)	50 / 50	4.0 (50)	100	50 / 50	4.0 (50)	100	50 / 50	4.0 (50)	100	50 / 50
13	4.0 (50)	50 / 50	3.9 (50)	98	50 / 50	4.0 (50)	100	50 / 50	3.9 (50)	98	50 / 50
14	4.1 (50)	50 / 50	4.1 (50)	100	50 / 50	4.1 (50)	100	50 / 50	4.1 (50)	100	50 / 50
18	4.1 (50)	50 / 50	4.2 (50)	102	50 / 50	4.1 (50)	100	50 / 50	4.0 (50)	98	50 / 50
22	4.2 (50)	50 / 50	4.2 (50)	100	50 / 50	4.1 (50)	98	50 / 50	4.0 (50)	95	50 / 50
26	4.1 (50)	50 / 50	4.4 (50)	107	50 / 50	4.4 (50)	107	50 / 50	4.3 (50)	105	50 / 50
30	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.3 (50)	102	50 / 50	4.2 (50)	100	50 / 50
34	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.3 (50)	102	50 / 50	4.2 (50)	100	50 / 50
38	4.3 (50)	50 / 50	4.4 (50)	102	50 / 50	4.3 (50)	100	50 / 50	4.2 (50)	98	50 / 50
42	4.4 (50)	50 / 50	4.5 (50)	102	50 / 50	4.4 (50)	100	50 / 50	4.3 (50)	98	50 / 50
46	4.5 (50)	50 / 50	4.5 (50)	100	50 / 50	4.5 (50)	100	50 / 50	4.4 (50)	98	50 / 50
50	4.4 (50)	50 / 50	4.4 (50)	100	50 / 50	4.4 (50)	100	50 / 50	4.2 (50)	95	50 / 50
54	4.4 (49)	49 / 50	4.5 (50)	102	50 / 50	4.4 (50)	100	50 / 50	4.3 (50)	98	50 / 50
58	4.5 (48)	48 / 50	4.5 (47)	100	50 / 50	4.5 (50)	100	50 / 50	4.3 (50)	96	50 / 50
62	4.5 (48)	48 / 50	4.6 (50)	102	50 / 50	4.6 (50)	102	50 / 50	4.4 (50)	98	50 / 50
66	4.5 (48)	48 / 50	4.6 (49)	102	49 / 50	4.6 (50)	102	50 / 50	4.4 (50)	98	50 / 50
70	4.7 (48)	48 / 50	4.7 (49)	100	49 / 50	4.6 (50)	98	50 / 50	4.5 (50)	96	50 / 50
74	4.5 (47)	47 / 50	4.7 (47)	104	47 / 50	4.6 (49)	102	49 / 50	4.4 (49)	98	49 / 50
78	4.6 (45)	45 / 50	4.8 (47)	104	47 / 50	4.7 (48)	102	48 / 50	4.5 (48)	98	48 / 50
82	4.7 (43)	43 / 50	4.7 (47)	100	47 / 50	4.7 (46)	100	46 / 50	4.6 (48)	98	48 / 50
86	4.5 (42)	42 / 50	4.8 (46)	107	46 / 50	4.7 (45)	104	45 / 50	4.5 (46)	100	46 / 50
90	4.6 (35)	35 / 50	4.8 (45)	104	45 / 50	4.7 (43)	102	43 / 50	4.5 (44)	98	44 / 50
94	4.6 (35)	35 / 50	4.8 (43)	104	43 / 50	4.7 (42)	102	42 / 50	4.3 (43)	93	43 / 50
98	4.6 (29)	29 / 50	4.6 (41)	100	41 / 50	4.5 (42)	98	42 / 50	4.4 (39)	96	39 / 50
102	4.5 (28)	28 / 50	4.6 (40)	102	40 / 50	4.5 (39)	100	39 / 50	4.4 (38)	98	38 / 50
104	4.9 (24)	25 / 50	4.7 (35)	96	37 / 50	4.5 (37)	92	37 / 50	4.6 (37)	94	37 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. FC. : Averaged food consumption (Unit : g).

TABLE 4 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2000 ppm			6325 ppm			20000 ppm		
	Av. FC.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>	Av. FC.	% of cont.	No. of Surviv. <50>
1	3.3 (50)	50 / 50	3.3 (50)	100	50 / 50	3.3 (50)	100	50 / 50	3.2 (50)	97	50 / 50
2	3.3 (50)	50 / 50	3.4 (50)	103	50 / 50	3.4 (50)	103	50 / 50	3.2 (50)	97	50 / 50
3	3.3 (50)	50 / 50	3.3 (50)	100	50 / 50	3.3 (50)	100	50 / 50	3.2 (50)	97	50 / 50
4	3.4 (50)	50 / 50	3.5 (50)	103	50 / 50	3.5 (50)	103	50 / 50	3.4 (50)	100	50 / 50
5	3.4 (50)	50 / 50	3.5 (50)	103	50 / 50	3.5 (50)	103	50 / 50	3.3 (50)	97	50 / 50
6	3.7 (50)	50 / 50	3.7 (50)	100	50 / 50	3.7 (50)	100	50 / 50	3.6 (50)	97	50 / 50
7	3.7 (50)	50 / 50	3.7 (50)	100	50 / 50	3.7 (50)	100	50 / 50	3.5 (49)	95	50 / 50
8	3.8 (50)	50 / 50	3.8 (50)	100	50 / 50	3.8 (50)	100	50 / 50	3.7 (50)	97	50 / 50
9	3.7 (50)	50 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50	3.7 (50)	100	50 / 50
10	3.8 (50)	50 / 50	3.9 (50)	103	50 / 50	3.8 (50)	100	50 / 50	3.7 (50)	97	50 / 50
11	3.7 (50)	50 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50	3.7 (50)	100	50 / 50
12	3.7 (50)	50 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50	3.6 (50)	97	50 / 50
13	3.5 (50)	50 / 50	3.5 (50)	100	50 / 50	3.6 (50)	103	50 / 50	3.4 (50)	97	50 / 50
14	3.7 (50)	50 / 50	3.6 (50)	97	50 / 50	3.6 (50)	97	50 / 50	3.6 (50)	97	50 / 50
18	3.5 (50)	50 / 50	3.6 (50)	103	50 / 50	3.6 (50)	103	50 / 50	3.5 (50)	100	50 / 50
22	3.8 (50)	50 / 50	3.9 (50)	103	50 / 50	3.9 (36)	103	50 / 50	3.6 (50)	95	50 / 50
26	3.7 (50)	50 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50	3.7 (50)	100	50 / 50
30	3.6 (50)	50 / 50	3.7 (50)	103	50 / 50	3.7 (50)	103	50 / 50	3.6 (50)	100	50 / 50
34	3.7 (50)	50 / 50	3.6 (50)	97	50 / 50	3.6 (50)	97	50 / 50	3.6 (50)	97	50 / 50
38	3.8 (50)	50 / 50	3.7 (50)	97	50 / 50	3.7 (49)	97	49 / 50	3.6 (50)	95	50 / 50
42	3.8 (50)	50 / 50	3.8 (50)	100	50 / 50	3.8 (49)	100	49 / 50	3.8 (50)	100	50 / 50
46	3.9 (50)	50 / 50	3.7 (50)	95	50 / 50	3.9 (49)	100	49 / 50	3.6 (50)	92	50 / 50
50	3.8 (50)	50 / 50	3.7 (49)	97	49 / 50	3.7 (49)	97	49 / 50	3.6 (50)	95	50 / 50
54	3.8 (50)	50 / 50	3.8 (49)	100	49 / 50	3.8 (49)	100	49 / 50	3.7 (49)	97	49 / 50
58	3.9 (50)	50 / 50	4.0 (49)	103	49 / 50	3.8 (49)	97	49 / 50	3.7 (49)	95	49 / 50
62	3.9 (48)	48 / 50	4.0 (49)	103	49 / 50	4.0 (49)	103	49 / 50	3.8 (47)	97	47 / 50
66	4.0 (46)	46 / 50	3.9 (49)	98	49 / 50	3.9 (49)	98	49 / 50	3.8 (47)	95	47 / 50
70	4.1 (44)	44 / 50	4.0 (49)	98	49 / 50	4.0 (49)	98	49 / 50	3.9 (47)	95	47 / 50
74	3.8 (43)	43 / 50	3.9 (47)	103	47 / 50	4.0 (49)	105	49 / 50	3.7 (44)	97	44 / 50
78	4.0 (43)	43 / 50	4.0 (47)	100	47 / 50	4.1 (48)	103	48 / 50	3.8 (42)	95	42 / 50
82	4.2 (40)	40 / 50	4.1 (43)	98	43 / 50	4.2 (48)	100	48 / 50	4.0 (40)	95	40 / 50
86	4.0 (39)	39 / 50	4.0 (40)	100	40 / 50	4.1 (47)	103	47 / 50	3.8 (38)	95	38 / 50
90	4.1 (38)	38 / 50	4.1 (35)	100	35 / 50	4.2 (46)	102	46 / 50	3.8 (34)	93	34 / 50
94	3.9 (38)	38 / 50	4.2 (34)	108	34 / 50	4.1 (44)	105	44 / 50	3.8 (32)	97	32 / 50
98	4.0 (37)	37 / 50	4.1 (27)	103	27 / 50	4.1 (41)	103	41 / 50	3.8 (31)	95	31 / 50
102	4.0 (36)	36 / 50	4.1 (25)	103	25 / 50	4.1 (38)	103	38 / 50	3.7 (28)	93	28 / 50
104	4.0 (36)	36 / 50	4.0 (23)	100	23 / 50	4.2 (31)	105	31 / 50	3.9 (26)	98	26 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. FC. : Averaged food consumption (Unit : g).

TABLE 5 WATER CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control			2000 ppm			6325 ppm			20000 ppm		
	Av. WC.		No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>
1	4.6 (50)		50 / 50	4.6 (50)	100	50 / 50	4.8 (50)	104	50 / 50	4.6 (50)	100	50 / 50
2	4.5 (50)		50 / 50	4.5 (50)	100	50 / 50	4.6 (50)	102	50 / 50	4.3 (50)	96	50 / 50
3	4.3 (50)		50 / 50	4.4 (50)	102	50 / 50	4.6 (49)	107	50 / 50	4.2 (50)	98	50 / 50
4	4.3 (50)		50 / 50	4.2 (50)	98	50 / 50	4.5 (49)	105	50 / 50	4.3 (50)	100	50 / 50
5	4.2 (50)		50 / 50	4.2 (50)	100	50 / 50	4.5 (50)	107	50 / 50	4.3 (50)	102	50 / 50
6	4.2 (49)		50 / 50	4.4 (50)	105	50 / 50	4.5 (49)	107	50 / 50	4.3 (50)	102	50 / 50
7	4.1 (50)		50 / 50	4.2 (50)	102	50 / 50	4.4 (50)	107	50 / 50	4.1 (50)	100	50 / 50
8	4.1 (50)		50 / 50	4.4 (50)	107	50 / 50	4.5 (50)	110	50 / 50	4.3 (50)	105	50 / 50
9	4.1 (50)		50 / 50	4.2 (50)	102	50 / 50	4.5 (50)	110	50 / 50	4.2 (50)	102	50 / 50
10	4.1 (50)		50 / 50	4.2 (50)	102	50 / 50	4.4 (50)	107	50 / 50	4.1 (50)	100	50 / 50
11	3.9 (50)		50 / 50	4.1 (50)	105	50 / 50	4.2 (50)	108	50 / 50	4.1 (50)	105	50 / 50
12	3.9 (50)		50 / 50	4.0 (50)	103	50 / 50	4.1 (50)	105	50 / 50	3.9 (50)	100	50 / 50
13	3.9 (50)		50 / 50	3.9 (50)	100	50 / 50	4.2 (50)	108	50 / 50	3.9 (50)	100	50 / 50
14	3.9 (50)		50 / 50	3.9 (50)	100	50 / 50	4.2 (50)	108	50 / 50	3.8 (50)	97	50 / 50
18	3.6 (50)		50 / 50	3.7 (50)	103	50 / 50	3.8 (50)	106	50 / 50	3.6 (50)	100	50 / 50
22	3.3 (50)		50 / 50	3.4 (50)	103	50 / 50	3.5 (50)	106	50 / 50	3.3 (50)	100	50 / 50
26	3.6 (50)		50 / 50	3.6 (50)	100	50 / 50	3.7 (50)	103	50 / 50	3.4 (50)	94	50 / 50
30	3.6 (50)		50 / 50	3.6 (50)	100	50 / 50	3.6 (50)	100	50 / 50	3.4 (50)	94	50 / 50
34	3.7 (50)		50 / 50	3.6 (50)	97	50 / 50	3.7 (50)	100	50 / 50	3.4 (50)	92	50 / 50
38	3.7 (50)		50 / 50	3.6 (50)	97	50 / 50	3.7 (50)	100	50 / 50	3.5 (50)	95	50 / 50
42	3.8 (50)		50 / 50	3.7 (50)	97	50 / 50	3.7 (50)	97	50 / 50	3.4 (50)	89	50 / 50
46	4.0 (50)		50 / 50	3.9 (50)	98	50 / 50	4.0 (50)	100	50 / 50	3.6 (50)	90	50 / 50
50	3.7 (50)		50 / 50	3.7 (50)	100	50 / 50	3.7 (50)	100	50 / 50	3.4 (50)	92	50 / 50
54	3.9 (49)		49 / 50	3.9 (50)	100	50 / 50	3.9 (50)	100	50 / 50	3.6 (50)	92	50 / 50
58	3.7 (48)		48 / 50	3.8 (50)	103	50 / 50	3.8 (50)	103	50 / 50	3.3 (50)	89	50 / 50
62	3.9 (48)		48 / 50	4.0 (50)	103	50 / 50	4.0 (50)	103	50 / 50	3.5 (50)	90	50 / 50
66	3.9 (48)		48 / 50	4.1 (49)	105	49 / 50	4.1 (49)	105	50 / 50	3.5 (50)	90	50 / 50
70	4.1 (48)		48 / 50	4.1 (49)	100	49 / 50	4.1 (49)	100	50 / 50	3.6 (50)	88	50 / 50
74	4.1 (47)		47 / 50	4.3 (47)	105	47 / 50	4.3 (48)	105	49 / 50	3.8 (49)	93	49 / 50
78	4.3 (45)		45 / 50	4.4 (47)	102	47 / 50	4.3 (47)	100	48 / 50	3.9 (48)	91	48 / 50
82	4.4 (43)		43 / 50	4.3 (47)	98	47 / 50	4.4 (46)	100	46 / 50	3.7 (48)	84	48 / 50
86	4.4 (42)		42 / 50	4.6 (46)	105	46 / 50	4.5 (45)	102	45 / 50	3.9 (46)	89	46 / 50
90	4.4 (33)		35 / 50	4.5 (43)	102	45 / 50	4.4 (43)	100	43 / 50	3.9 (44)	89	44 / 50
94	4.4 (34)		35 / 50	4.8 (42)	109	43 / 50	4.6 (42)	105	42 / 50	3.9 (43)	89	43 / 50
98	4.6 (26)		29 / 50	4.5 (38)	98	41 / 50	4.4 (42)	96	42 / 50	3.9 (39)	85	39 / 50
102	4.4 (27)		28 / 50	4.8 (39)	109	40 / 50	4.4 (38)	100	39 / 50	4.1 (38)	93	38 / 50
104	4.9 (25)		25 / 50	4.4 (36)	90	37 / 50	4.3 (36)	88	37 / 50	4.2 (37)	86	37 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. WC. : Averaged water consumption (Unit : g).

TABLE 6 WATER CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2000 ppm			6325 ppm			20000 ppm		
	Av. WC.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>	Av. WC.	% of cont.	No. of Surviv. <50>
1	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.3 (50)	102	50 / 50	4.0 (50)	95	50 / 50
2	4.1 (50)	50 / 50	4.3 (50)	105	50 / 50	4.4 (50)	107	50 / 50	4.1 (50)	100	50 / 50
3	4.2 (50)	50 / 50	4.2 (49)	100	50 / 50	4.3 (50)	102	50 / 50	4.1 (49)	98	50 / 50
4	4.3 (49)	50 / 50	4.8 (49)	112	50 / 50	4.6 (50)	107	50 / 50	4.2 (50)	98	50 / 50
5	4.4 (50)	50 / 50	4.5 (49)	102	50 / 50	4.6 (50)	105	50 / 50	4.3 (50)	98	50 / 50
6	4.5 (50)	50 / 50	4.5 (48)	100	50 / 50	4.7 (50)	104	50 / 50	4.3 (50)	96	50 / 50
7	4.4 (49)	50 / 50	4.7 (50)	107	50 / 50	4.6 (49)	105	50 / 50	4.1 (50)	93	50 / 50
8	4.5 (49)	50 / 50	4.8 (50)	107	50 / 50	4.9 (48)	109	50 / 50	4.3 (50)	96	50 / 50
9	4.7 (50)	50 / 50	4.7 (50)	100	50 / 50	4.8 (49)	102	50 / 50	4.2 (50)	89	50 / 50
10	4.6 (50)	50 / 50	5.0 (48)	109	50 / 50	4.7 (48)	102	50 / 50	4.3 (50)	93	50 / 50
11	4.4 (50)	50 / 50	4.8 (50)	109	50 / 50	4.6 (50)	105	50 / 50	4.1 (50)	93	50 / 50
12	4.6 (50)	50 / 50	4.7 (49)	102	50 / 50	4.8 (50)	104	50 / 50	4.3 (49)	93	50 / 50
13	4.5 (50)	50 / 50	4.7 (50)	104	50 / 50	4.5 (48)	100	50 / 50	4.2 (50)	93	50 / 50
14	4.3 (50)	50 / 50	4.3 (48)	100	50 / 50	4.3 (48)	100	50 / 50	4.0 (50)	93	50 / 50
18	4.1 (50)	50 / 50	4.4 (50)	107	50 / 50	4.6 (49)	112	50 / 50	4.0 (50)	98	50 / 50
22	4.2 (50)	50 / 50	4.3 (50)	102	50 / 50	4.3 (50)	102	50 / 50	3.9 (50)	93	50 / 50
26	4.4 (50)	50 / 50	4.4 (50)	100	50 / 50	4.5 (49)	102	50 / 50	4.0 (50)	91	50 / 50
30	4.1 (49)	50 / 50	4.1 (50)	100	50 / 50	4.3 (50)	105	50 / 50	3.8 (50)	93	50 / 50
34	4.2 (50)	50 / 50	4.2 (49)	100	50 / 50	4.0 (50)	95	50 / 50	3.7 (50)	88	50 / 50
38	4.0 (50)	50 / 50	4.2 (50)	105	50 / 50	4.1 (49)	103	49 / 50	3.8 (50)	95	50 / 50
42	4.0 (50)	50 / 50	4.1 (50)	103	50 / 50	4.0 (49)	100	49 / 50	3.7 (50)	93	50 / 50
46	4.2 (50)	50 / 50	4.2 (50)	100	50 / 50	4.2 (49)	100	49 / 50	3.9 (50)	93	50 / 50
50	4.0 (50)	50 / 50	3.7 (49)	93	49 / 50	3.9 (49)	98	49 / 50	3.7 (50)	93	50 / 50
54	3.9 (49)	50 / 50	4.0 (49)	103	49 / 50	4.0 (49)	103	49 / 50	3.8 (49)	97	49 / 50
58	4.0 (49)	50 / 50	3.9 (49)	98	49 / 50	4.0 (49)	100	49 / 50	3.6 (49)	90	49 / 50
62	3.9 (48)	48 / 50	4.0 (49)	103	49 / 50	4.0 (49)	103	49 / 50	3.8 (47)	97	47 / 50
66	4.0 (46)	46 / 50	3.8 (49)	95	49 / 50	3.9 (49)	98	49 / 50	3.8 (47)	95	47 / 50
70	3.9 (43)	44 / 50	4.0 (49)	103	49 / 50	4.0 (49)	103	49 / 50	3.7 (47)	95	47 / 50
74	4.1 (43)	43 / 50	4.2 (47)	102	47 / 50	4.1 (49)	100	49 / 50	3.7 (44)	90	44 / 50
78	4.1 (42)	43 / 50	4.2 (47)	102	47 / 50	4.2 (48)	102	48 / 50	3.7 (42)	90	42 / 50
82	4.3 (40)	40 / 50	4.1 (43)	95	43 / 50	4.3 (48)	100	48 / 50	3.8 (40)	88	40 / 50
86	4.2 (39)	39 / 50	4.3 (40)	102	40 / 50	4.1 (47)	98	47 / 50	3.8 (38)	90	38 / 50
90	4.1 (38)	38 / 50	4.2 (35)	102	35 / 50	4.2 (46)	102	46 / 50	3.7 (34)	90	34 / 50
94	4.2 (38)	38 / 50	4.5 (33)	107	34 / 50	4.3 (44)	102	44 / 50	3.9 (32)	93	32 / 50
98	4.2 (37)	37 / 50	4.2 (26)	100	27 / 50	4.1 (41)	98	41 / 50	4.1 (31)	98	31 / 50
102	4.1 (35)	36 / 50	4.4 (24)	107	25 / 50	4.3 (38)	105	38 / 50	3.9 (28)	95	28 / 50
104	4.3 (36)	36 / 50	4.5 (23)	105	23 / 50	4.3 (31)	100	31 / 50	4.0 (25)	93	26 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. WC. : Averaged water consumption (Unit : g).

TABLE 7 BIOCHEMISTRY OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals	36	23	30	26
ALP (IU/L)	210 ± 74	192 ± 62	179 ± 66	257 ± 99 *
CK (IU/L)	118 ± 124	76 ± 52 *	287 ± 1030	131 ± 221

Mean ± S.D.

Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 8 URINALYSIS OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name		Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals		36	25	37	28
	Grade				
pH	5.0	0	0	0	0
	6.0	0	1	1	2
	6.5	1	0	4	6
	7.0	4	4	10	6
	7.5	5	2	5	5
	8.0	17	15	14	8
	8.5	9	3	3	1
	Chi square test				*
Ketone body	−	5	2	5	0
	±	24	20	28	12
	+	6	1	3	9
	2+	1	2	1	5
	3+	0	0	0	2
	4+	0	0	0	0
	Chi square test				**

Significant difference: * : p≦0.05 ** : p≦0.01

TABLE 9 ORGAN WEIGHTS OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals	25	37	37	37
Body weight (g)	48.0 ± 5.0	46.5 ± 8.3	44.0 ± 7.2	46.4 ± 6.8
Heart (g)	0.211 ± 0.018	0.218 ± 0.023	0.213 ± 0.024	0.215 ± 0.034
Heart (%)	0.445 ± 0.051	0.489 ± 0.154	0.493 ± 0.074 *	0.469 ± 0.077
Kidneys (g)	0.630 ± 0.048	0.656 ± 0.087	0.728 ± 0.462	0.925 ± 1.289
Kidneys (%)	1.328 ± 0.190	1.482 ± 0.613	1.737 ± 1.373 **	2.036 ± 2.849
Liver (g)	1.633 ± 0.188	1.716 ± 0.427	2.000 ± 0.951	1.838 ± 0.678
Liver (%)	3.433 ± 0.497	3.778 ± 1.042	4.678 ± 2.487 *	4.118 ± 2.058

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 10 ORGAN WEIGHTS OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals	36	23	31	26
Body weight (g)	30.9 ± 3.9	30.8 ± 3.4	32.4 ± 4.1	29.4 ± 4.0
Kidneys (g)	0.420 ± 0.040	0.438 ± 0.048	0.471 ± 0.144	0.454 ± 0.085
Kidneys (%)	1.373 ± 0.166	1.426 ± 0.122	1.485 ± 0.562	1.573 ± 0.416 *

Mean ± S.D.
Significant difference: * : p≦0.05 ** : p≦0.01 Test of Dunnett

TABLE 11 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm	Peto	Cochran-Armitage
Number of examined animals	50	50	50	50	test	test
lung	<50>	<50>	<50>	<50>		
bronchiolar-alveolar carcinoma	0 (0 %)	1 (2 %)	2 (4 %)	4 (8 %)	↑	↑

Significant difference * : p≦0.05 ** : p≦0.01 Fisher's exact test for neoplastic lesion
↑(↓) : p≦0.05 ↑↑(↓↓) : p≦0.01 Peto or Cochran-Armitage test for neoplastic lesion
< > : Number of animals examined at the site

TABLE 12 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : BDF1 FEMALE MICE

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Lung	1597			
Bronchiolar-alveolar adenoma		56	3.5	0 - 10
Bronchiolar-alveolar carcinoma		47	2.9	0 - 8

32 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

TABLE 13 CAUSE OF DEATH OF MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

	Male				Female			
Group name	Control	2000 ppm	6325 ppm	20000 ppm	Control	2000 ppm	6325 ppm	20000 ppm
Number of dead or moribund animals	25	13	13	13	14	27	19	24
No microscopical confirmation	1	0	0	0	1	1	0	0
Cardiovascular lesion	0	0	0	2	0	0	0	0
Renal lesion	0	0	1	0	0	0	0	0
Reproductive system lesion	0	0	1	0	0	0	0	1
Central nervous system lesion	0	0	0	0	1	0	0	0
Urinary retention	2	3	0	0	0	1	1	0
Hydronephrosis	0	1	0	0	0	0	0	0
Tumor death ： leukemia	6	2	5	1	2	7	7	8
subcutis	1	0	1	0	0	0	0	0
nasal cavity	1	0	0	0	0	0	0	0
lung	1	1	0	1	0	1	0	1
lymph node	0	0	0	1	0	0	0	0
spleen	0	1	0	1	0	2	1	0
heart	0	0	0	1	0	0	0	0
liver	12	4	5	4	1	2	1	1
urinary bladder	0	1	0	0	0	0	0	0
epididymis	1	0	0	0	—	—	—	—
pituitary gland	0	0	0	0	0	2	2	1
uterus	—	—	—	—	8	10	7	12
mammary gland	0	0	0	0	0	1	0	0
peripheral nerves	0	0	0	1	1	0	0	0
retroperitoneum	0	0	0	1	0	0	0	0

FIGURES

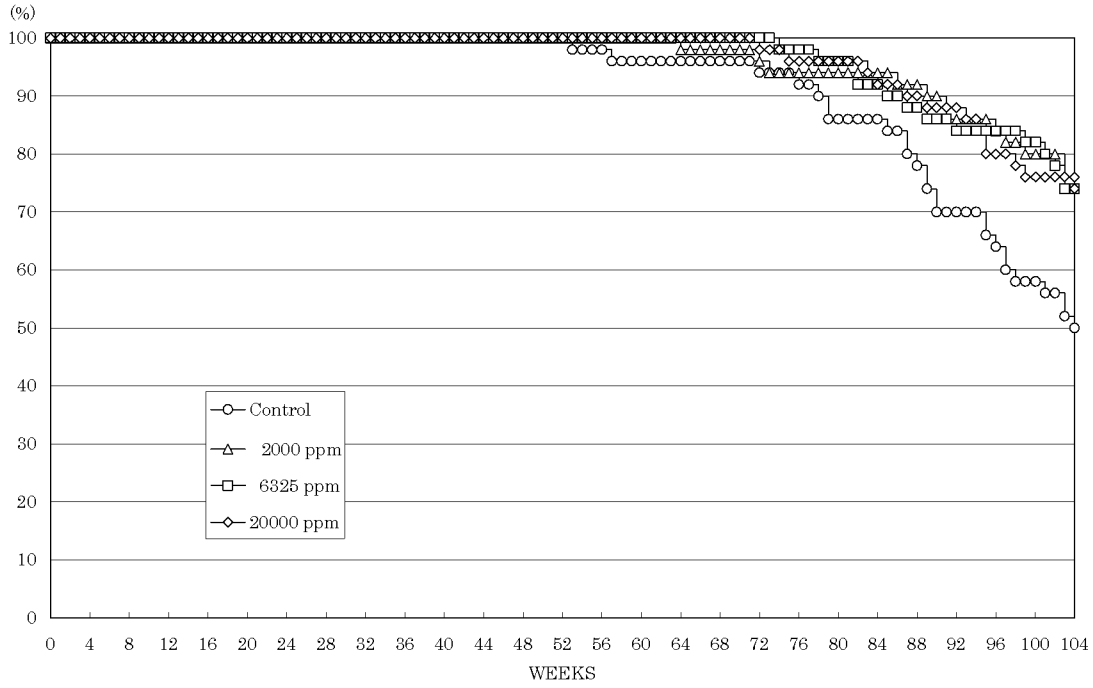

FIGURE 1 SURVIVAL ANIMAL RATE OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

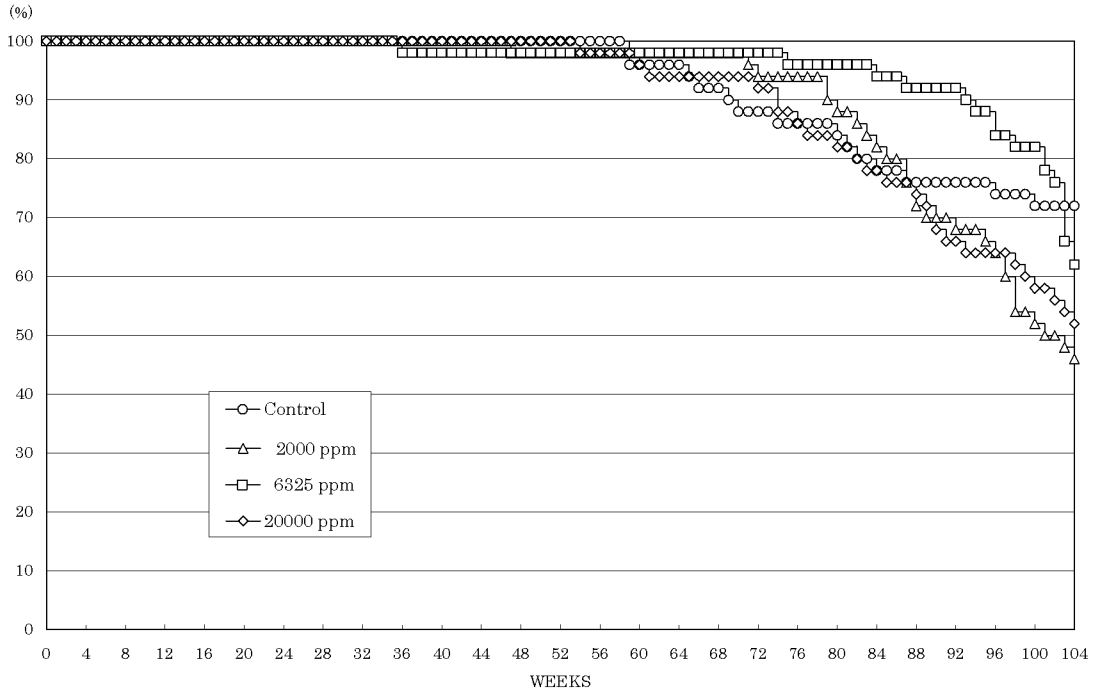

FIGURE 2 SURVIVAL ANIMAL RATE OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

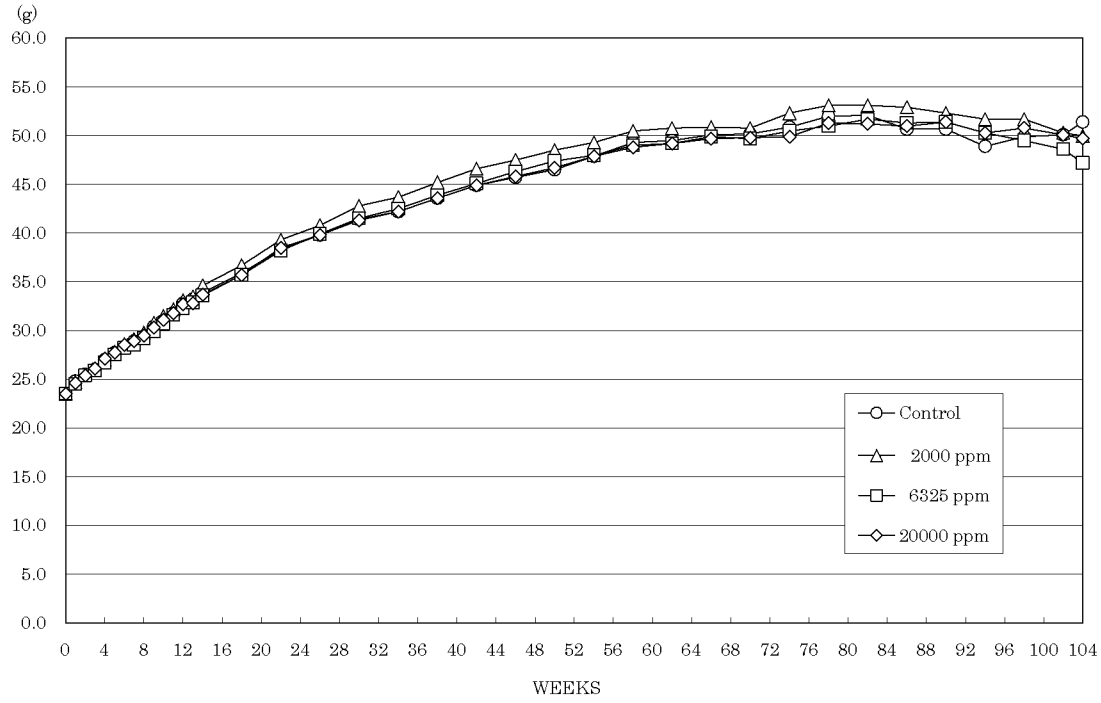

FIGURE 3 BODY WEIGHT CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

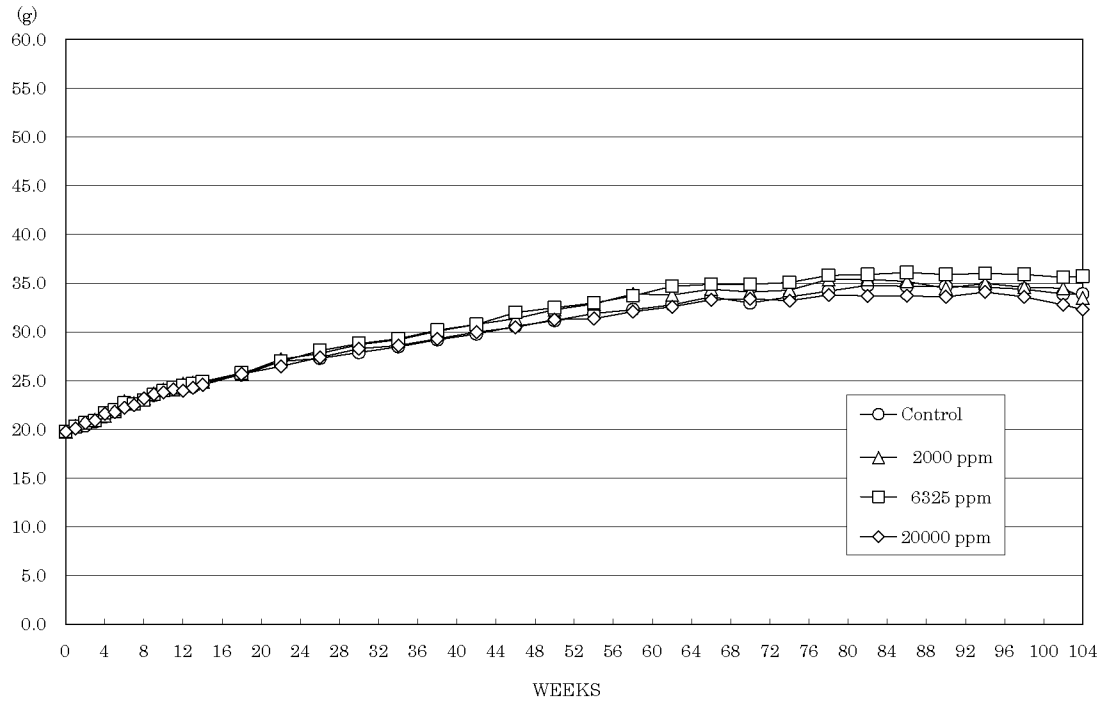

FIGURE 4 BODY WEIGHT CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

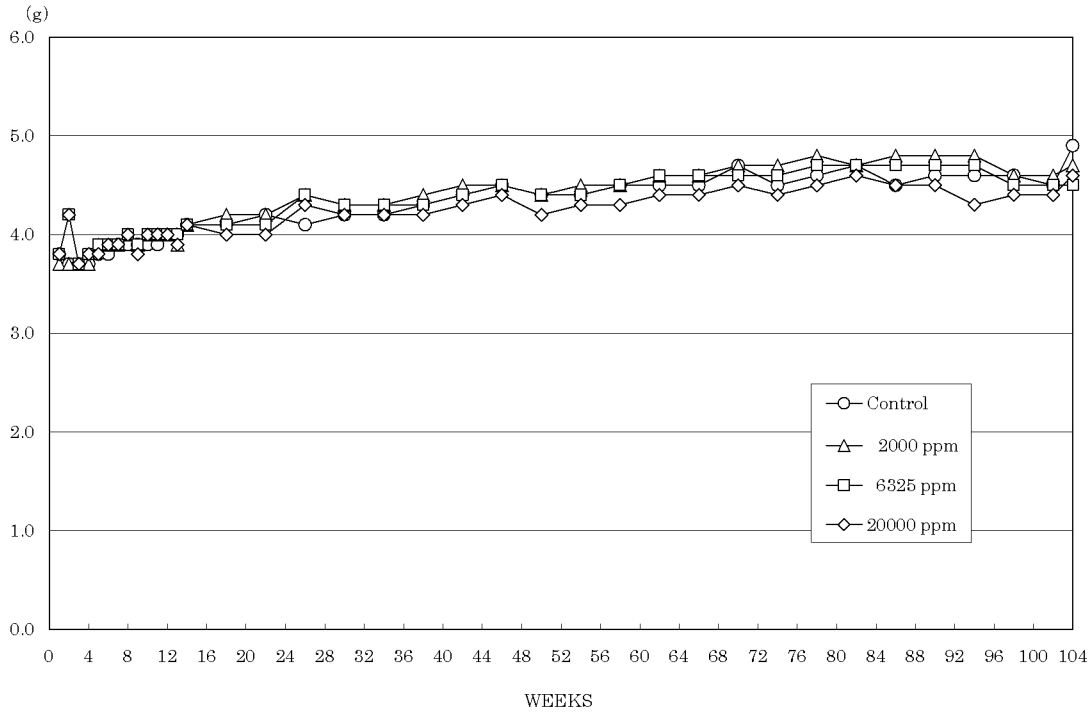

FIGURE 5 FOOD CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

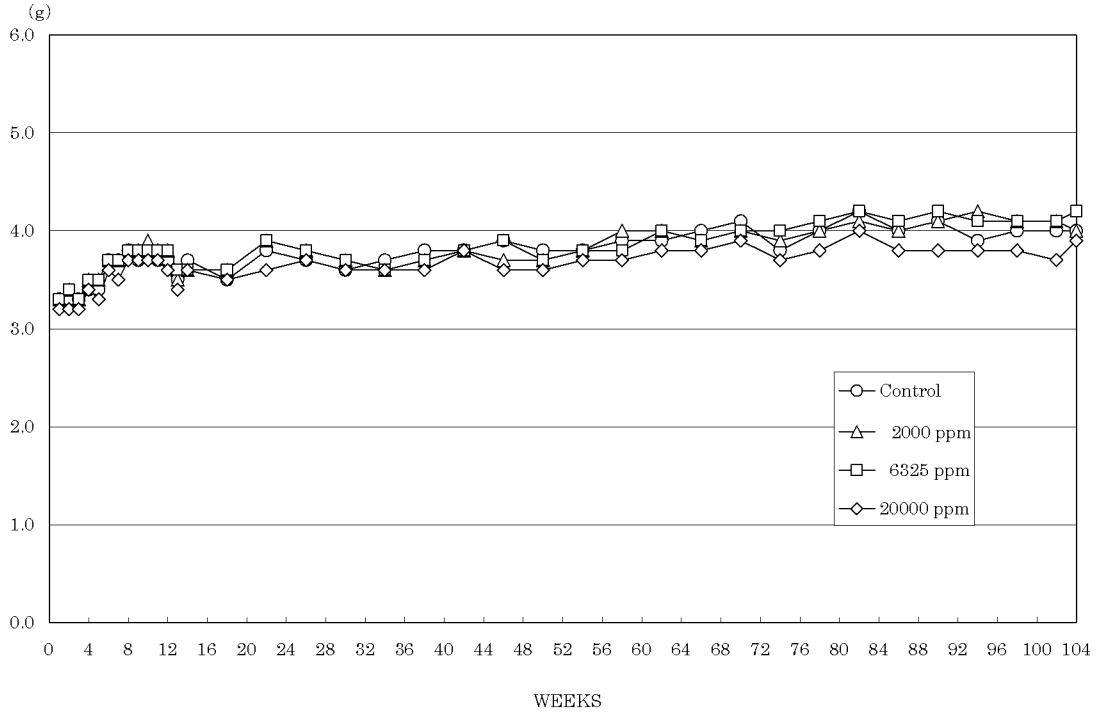

FIGURE 6 FOOD CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

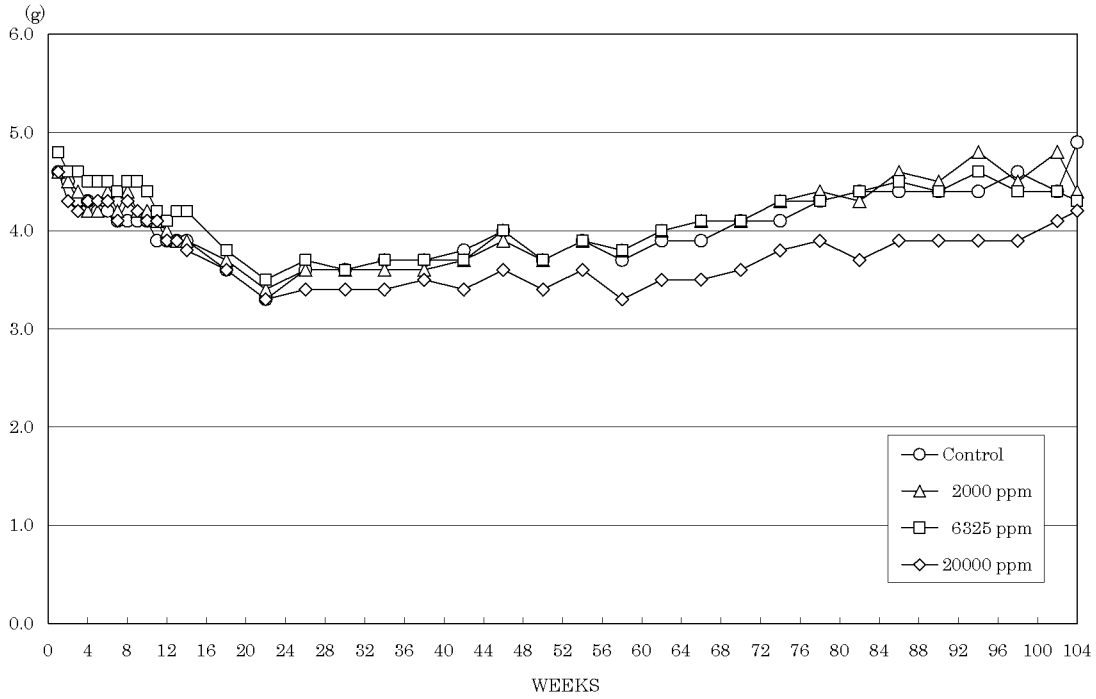

FIGURE 7 WATER CONSUMPTION CHANGES OF MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

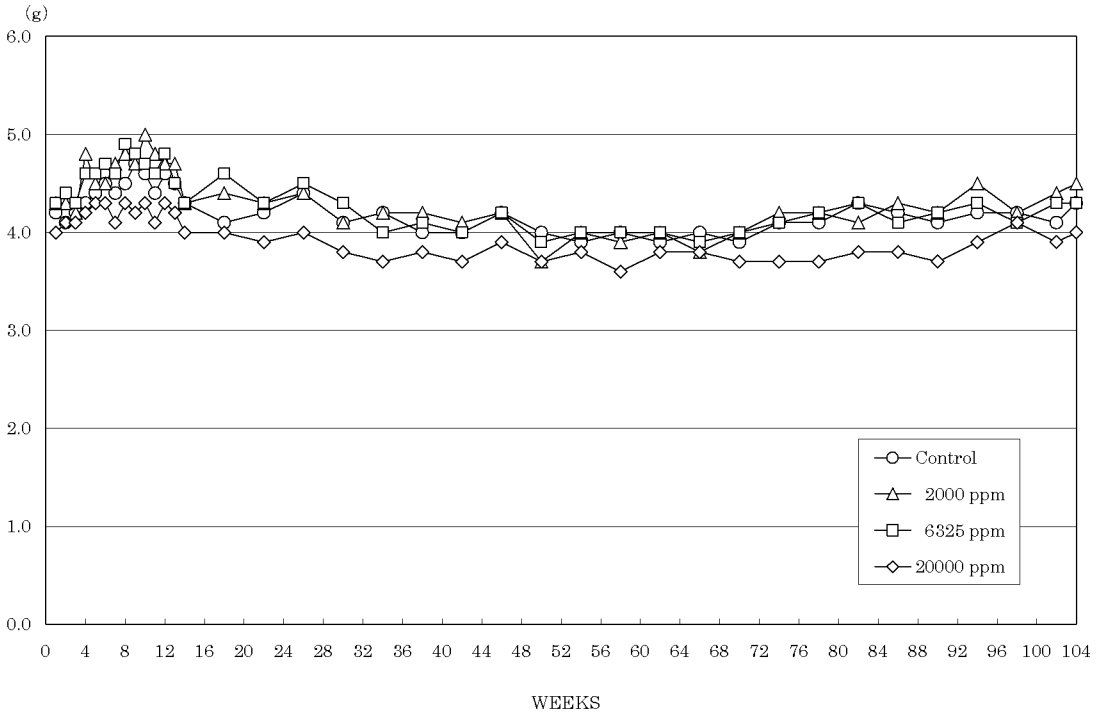

FIGURE 8 WATER CONSUMPTION CHANGES OF FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE