アセト酢酸メチルのラットを用いた
経口投与によるがん原性試験（混水試験）報告書

試験番号：0448

TABLES

TABLES

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TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS 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	125 (50)	50 / 50	125 (50)	100	50 / 50	125 (50)	100	50 / 50	125 (50)	100	50 / 50
1	155 (50)	50 / 50	153 (50)	99	50 / 50	152 (50)	98	50 / 50	147 (50)	95	50 / 50
2	183 (50)	50 / 50	183 (50)	100	50 / 50	182 (50)	99	50 / 50	176 (50)	96	50 / 50
3	206 (50)	50 / 50	208 (50)	101	50 / 50	206 (50)	100	50 / 50	201 (50)	98	50 / 50
4	223 (50)	50 / 50	225 (50)	101	50 / 50	223 (50)	100	50 / 50	215 (50)	96	50 / 50
5	238 (50)	50 / 50	240 (50)	101	50 / 50	236 (50)	99	50 / 50	230 (50)	97	50 / 50
6	249 (50)	50 / 50	251 (50)	101	50 / 50	246 (50)	99	50 / 50	239 (50)	96	50 / 50
7	259 (50)	50 / 50	262 (50)	101	50 / 50	255 (50)	98	50 / 50	248 (50)	96	50 / 50
8	268 (50)	50 / 50	272 (50)	101	50 / 50	265 (50)	99	50 / 50	256 (50)	96	50 / 50
9	277 (50)	50 / 50	281 (50)	101	50 / 50	274 (50)	99	50 / 50	264 (50)	95	50 / 50
10	284 (50)	50 / 50	288 (50)	101	50 / 50	279 (50)	98	50 / 50	268 (50)	94	50 / 50
11	291 (50)	50 / 50	294 (50)	101	50 / 50	284 (50)	98	50 / 50	272 (50)	93	50 / 50
12	297 (50)	50 / 50	300 (50)	101	50 / 50	289 (50)	97	50 / 50	275 (50)	93	50 / 50
13	301 (50)	50 / 50	305 (50)	101	50 / 50	293 (50)	97	50 / 50	280 (50)	93	50 / 50
14	304 (50)	50 / 50	308 (50)	101	50 / 50	297 (50)	98	50 / 50	284 (50)	93	50 / 50
18	325 (50)	50 / 50	329 (50)	101	50 / 50	317 (50)	98	50 / 50	300 (50)	92	50 / 50
22	340 (50)	50 / 50	343 (50)	101	50 / 50	328 (50)	96	50 / 50	308 (50)	91	50 / 50
26	351 (50)	50 / 50	352 (50)	100	50 / 50	337 (50)	96	50 / 50	314 (50)	89	50 / 50
30	361 (50)	50 / 50	362 (50)	100	50 / 50	346 (50)	96	50 / 50	319 (50)	88	50 / 50
34	370 (50)	50 / 50	370 (50)	100	50 / 50	353 (50)	95	50 / 50	325 (50)	88	50 / 50
38	376 (50)	50 / 50	376 (49)	100	49 / 50	357 (49)	95	49 / 50	326 (50)	87	50 / 50
42	382 (50)	50 / 50	381 (49)	100	49 / 50	361 (49)	95	49 / 50	328 (49)	86	49 / 50
46	389 (50)	50 / 50	389 (49)	100	49 / 50	367 (49)	94	49 / 50	336 (47)	86	47 / 50
50	396 (50)	50 / 50	396 (49)	100	49 / 50	372 (49)	94	49 / 50	341 (46)	86	46 / 50
54	397 (50)	50 / 50	395 (48)	99	48 / 50	371 (49)	93	49 / 50	340 (46)	86	46 / 50
58	404 (50)	50 / 50	403 (48)	100	48 / 50	379 (49)	94	49 / 50	345 (46)	85	46 / 50
62	409 (50)	50 / 50	408 (48)	100	48 / 50	383 (49)	94	49 / 50	347 (45)	85	45 / 50
66	411 (50)	50 / 50	410 (48)	100	48 / 50	385 (49)	94	49 / 50	353 (44)	86	44 / 50
70	415 (48)	48 / 50	414 (47)	100	47 / 50	390 (49)	94	49 / 50	354 (44)	85	44 / 50
74	418 (47)	47 / 50	417 (46)	100	46 / 50	391 (49)	94	49 / 50	356 (44)	85	44 / 50
78	417 (46)	46 / 50	419 (46)	100	46 / 50	393 (49)	94	49 / 50	357 (44)	86	44 / 50
82	423 (45)	45 / 50	421 (46)	100	46 / 50	395 (49)	93	49 / 50	356 (44)	84	44 / 50
86	422 (45)	45 / 50	418 (46)	99	46 / 50	397 (47)	94	47 / 50	355 (44)	84	44 / 50
90	426 (44)	44 / 50	417 (46)	98	46 / 50	395 (46)	93	46 / 50	351 (43)	82	43 / 50
94	426 (42)	42 / 50	410 (45)	96	45 / 50	392 (46)	92	46 / 50	350 (42)	82	42 / 50
98	426 (40)	40 / 50	406 (44)	95	44 / 50	383 (43)	90	43 / 50	345 (42)	81	42 / 50
102	419 (39)	39 / 50	398 (42)	95	42 / 50	374 (41)	89	41 / 50	338 (41)	81	41 / 50
104	411 (38)	38 / 50	389 (41)	95	41 / 50	369 (40)	90	40 / 50	335 (39)	82	39 / 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 RATS 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	98 (50)	50 / 50	98 (50)	100	50 / 50	98 (50)	100	50 / 50	98 (50)	100	50 / 50
1	114 (50)	50 / 50	112 (50)	98	50 / 50	111 (50)	97	50 / 50	107 (50)	94	50 / 50
2	124 (50)	50 / 50	123 (50)	99	50 / 50	124 (50)	100	50 / 50	120 (50)	97	50 / 50
3	134 (50)	50 / 50	133 (50)	99	50 / 50	133 (50)	99	50 / 50	130 (50)	97	50 / 50
4	139 (50)	50 / 50	140 (50)	101	50 / 50	141 (50)	101	50 / 50	136 (50)	98	50 / 50
5	146 (50)	50 / 50	146 (50)	100	50 / 50	147 (50)	101	50 / 50	142 (50)	97	50 / 50
6	149 (50)	50 / 50	150 (50)	101	50 / 50	151 (50)	101	50 / 50	146 (50)	98	50 / 50
7	153 (50)	50 / 50	154 (50)	101	50 / 50	154 (50)	101	50 / 50	149 (50)	97	50 / 50
8	156 (50)	50 / 50	157 (50)	101	50 / 50	157 (50)	101	50 / 50	151 (50)	97	50 / 50
9	160 (50)	50 / 50	160 (50)	100	50 / 50	161 (50)	101	50 / 50	154 (50)	96	50 / 50
10	163 (50)	50 / 50	163 (50)	100	50 / 50	164 (50)	101	50 / 50	157 (50)	96	50 / 50
11	166 (50)	50 / 50	166 (50)	100	50 / 50	166 (50)	100	50 / 50	158 (50)	95	50 / 50
12	168 (50)	50 / 50	168 (50)	100	50 / 50	167 (50)	99	50 / 50	160 (50)	95	50 / 50
13	169 (50)	50 / 50	169 (50)	100	50 / 50	168 (50)	99	50 / 50	161 (50)	95	50 / 50
14	171 (50)	50 / 50	171 (50)	100	50 / 50	170 (50)	99	50 / 50	164 (50)	96	50 / 50
18	177 (50)	50 / 50	176 (50)	99	50 / 50	174 (50)	98	50 / 50	165 (50)	93	50 / 50
22	184 (50)	50 / 50	183 (50)	99	50 / 50	181 (50)	98	50 / 50	172 (50)	93	50 / 50
26	191 (50)	50 / 50	188 (50)	98	50 / 50	187 (50)	98	50 / 50	176 (50)	92	50 / 50
30	195 (50)	50 / 50	193 (50)	99	50 / 50	191 (50)	98	50 / 50	180 (49)	92	49 / 50
34	200 (50)	50 / 50	197 (50)	99	50 / 50	194 (50)	97	50 / 50	181 (49)	91	49 / 50
38	202 (50)	50 / 50	198 (50)	98	50 / 50	195 (50)	97	50 / 50	181 (49)	90	49 / 50
42	206 (50)	50 / 50	203 (50)	99	50 / 50	198 (50)	96	50 / 50	183 (48)	89	48 / 50
46	210 (49)	49 / 50	206 (50)	98	50 / 50	201 (50)	96	50 / 50	184 (48)	88	48 / 50
50	215 (49)	49 / 50	210 (50)	98	50 / 50	205 (50)	95	50 / 50	188 (45)	87	45 / 50
54	220 (49)	49 / 50	213 (50)	97	50 / 50	206 (50)	94	50 / 50	188 (44)	85	44 / 50
58	224 (49)	49 / 50	218 (50)	97	50 / 50	209 (50)	93	50 / 50	190 (44)	85	44 / 50
62	230 (49)	49 / 50	222 (50)	97	50 / 50	213 (50)	93	50 / 50	192 (44)	83	44 / 50
66	233 (49)	49 / 50	226 (50)	97	50 / 50	215 (50)	92	50 / 50	195 (44)	84	44 / 50
70	239 (49)	49 / 50	231 (50)	97	50 / 50	219 (50)	92	50 / 50	195 (43)	82	43 / 50
74	246 (48)	48 / 50	235 (50)	96	50 / 50	225 (49)	91	49 / 50	197 (42)	80	42 / 50
78	248 (48)	48 / 50	237 (50)	96	50 / 50	223 (48)	90	48 / 50	199 (40)	80	40 / 50
82	253 (47)	47 / 50	241 (50)	95	50 / 50	228 (48)	90	48 / 50	205 (37)	81	37 / 50
86	254 (46)	46 / 50	244 (50)	96	50 / 50	230 (45)	91	45 / 50	200 (34)	79	34 / 50
90	258 (41)	41 / 50	249 (50)	97	50 / 50	232 (43)	90	43 / 50	200 (32)	78	32 / 50
94	262 (40)	40 / 50	252 (49)	96	49 / 50	234 (43)	89	43 / 50	201 (31)	77	31 / 50
98	267 (39)	39 / 50	257 (47)	96	47 / 50	238 (41)	89	41 / 50	203 (28)	76	28 / 50
102	267 (38)	38 / 50	256 (43)	96	43 / 50	238 (40)	89	40 / 50	203 (25)	76	25 / 50
104	267 (38)	38 / 50	256 (43)	96	43 / 50	237 (40)	89	40 / 50	204 (25)	76	25 / 50

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

TABLE 3 FOOD CONSUMPTION CHANGES OF MALE RATS 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	13.5 (50)	50 / 50	13.2 (50)	98	50 / 50	12.9 (50)	96	50 / 50	11.7 (50)	87	50 / 50
2	14.6 (50)	50 / 50	14.5 (50)	99	50 / 50	14.0 (50)	96	50 / 50	13.4 (50)	92	50 / 50
3	15.3 (50)	50 / 50	15.5 (50)	101	50 / 50	14.9 (50)	97	50 / 50	14.4 (49)	94	50 / 50
4	15.1 (50)	50 / 50	15.1 (50)	100	50 / 50	14.7 (50)	97	50 / 50	14.1 (50)	93	50 / 50
5	15.3 (50)	50 / 50	15.3 (50)	100	50 / 50	14.7 (50)	96	50 / 50	14.3 (50)	93	50 / 50
6	14.7 (50)	50 / 50	14.9 (50)	101	50 / 50	14.2 (50)	97	50 / 50	13.6 (50)	93	50 / 50
7	14.8 (50)	50 / 50	15.1 (50)	102	50 / 50	14.3 (50)	97	50 / 50	13.7 (50)	93	50 / 50
8	14.9 (50)	50 / 50	15.1 (50)	101	50 / 50	14.2 (50)	95	50 / 50	13.5 (50)	91	50 / 50
9	14.8 (50)	50 / 50	15.2 (50)	103	50 / 50	14.2 (50)	96	50 / 50	13.6 (48)	92	50 / 50
10	14.7 (50)	50 / 50	14.8 (50)	101	50 / 50	13.9 (50)	95	50 / 50	13.3 (50)	90	50 / 50
11	14.6 (50)	50 / 50	14.5 (50)	99	50 / 50	13.9 (50)	95	50 / 50	13.1 (50)	90	50 / 50
12	14.4 (50)	50 / 50	14.4 (50)	100	50 / 50	13.7 (50)	95	50 / 50	12.9 (50)	90	50 / 50
13	14.5 (50)	50 / 50	14.7 (50)	101	50 / 50	14.0 (50)	97	50 / 50	13.1 (50)	90	50 / 50
14	13.8 (50)	50 / 50	13.9 (50)	101	50 / 50	13.3 (50)	96	50 / 50	12.4 (50)	90	50 / 50
18	14.1 (50)	50 / 50	14.3 (50)	101	50 / 50	13.6 (50)	96	50 / 50	12.7 (50)	90	50 / 50
20	14.2 (50)	50 / 50	14.3 (50)	101	50 / 50	13.5 (50)	95	50 / 50	12.6 (50)	89	50 / 50
22	14.6 (50)	50 / 50	14.8 (50)	101	50 / 50	14.1 (50)	97	50 / 50	13.0 (50)	89	50 / 50
26	14.8 (50)	50 / 50	14.5 (50)	98	50 / 50	14.0 (50)	95	50 / 50	12.8 (50)	86	50 / 50
30	14.5 (50)	50 / 50	14.6 (50)	101	50 / 50	14.1 (50)	97	50 / 50	12.9 (50)	89	50 / 50
34	14.5 (50)	50 / 50	14.5 (50)	100	50 / 50	13.9 (50)	96	50 / 50	12.8 (50)	88	50 / 50
38	14.1 (50)	50 / 50	14.4 (49)	102	49 / 50	13.7 (49)	97	49 / 50	12.5 (50)	89	50 / 50
42	14.6 (50)	50 / 50	14.7 (49)	101	49 / 50	14.2 (49)	97	49 / 50	12.8 (49)	88	49 / 50
46	14.8 (50)	50 / 50	15.1 (49)	102	49 / 50	14.4 (49)	97	49 / 50	13.2 (47)	89	47 / 50
50	14.9 (50)	50 / 50	15.1 (49)	101	49 / 50	14.2 (49)	95	49 / 50	13.3 (46)	89	46 / 50
54	14.6 (50)	50 / 50	15.0 (48)	103	48 / 50	14.5 (49)	99	49 / 50	13.3 (46)	91	46 / 50
58	14.8 (50)	50 / 50	14.9 (48)	101	48 / 50	14.3 (49)	97	49 / 50	13.2 (46)	89	46 / 50
62	15.3 (50)	50 / 50	15.8 (48)	103	48 / 50	15.2 (49)	99	49 / 50	13.7 (45)	90	45 / 50
66	15.4 (50)	50 / 50	15.6 (48)	101	48 / 50	15.0 (49)	97	49 / 50	13.7 (44)	89	44 / 50
70	15.2 (48)	48 / 50	15.3 (47)	101	47 / 50	14.8 (49)	97	49 / 50	13.7 (44)	90	44 / 50
74	15.2 (47)	47 / 50	15.3 (46)	101	46 / 50	14.7 (49)	97	49 / 50	13.4 (44)	88	44 / 50
78	15.2 (46)	46 / 50	15.6 (46)	103	46 / 50	14.9 (49)	98	49 / 50	13.8 (44)	91	44 / 50
82	15.2 (45)	45 / 50	15.3 (46)	101	46 / 50	14.6 (49)	96	49 / 50	13.3 (44)	88	44 / 50
86	15.2 (45)	45 / 50	15.3 (46)	101	46 / 50	14.6 (47)	96	47 / 50	13.3 (44)	88	44 / 50
90	15.5 (44)	44 / 50	15.3 (46)	99	46 / 50	14.5 (46)	94	46 / 50	13.1 (43)	85	43 / 50
94	14.8 (42)	42 / 50	14.4 (45)	97	45 / 50	14.2 (46)	96	46 / 50	12.8 (42)	86	42 / 50
98	15.1 (40)	40 / 50	14.5 (44)	96	44 / 50	14.2 (43)	94	43 / 50	12.8 (41)	85	42 / 50
102	15.1 (38)	39 / 50	14.4 (42)	95	42 / 50	14.2 (41)	94	41 / 50	12.9 (41)	85	41 / 50
104	14.6 (38)	38 / 50	13.6 (41)	93	41 / 50	14.0 (40)	96	40 / 50	12.4 (39)	85	39 / 50

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

TABLE 4 FOOD CONSUMPTION CHANGES OF FEMALE RATS 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.	Av. FC.	% of cont.	No. of Surviv.	Av. FC.	% of cont.	No. of Surviv.	Av. FC.	% of cont.	No. of Surviv.
	<50>		<50>			<50>			<50>		
1	10.3 (50)	50 / 50	9.9 (50)	96	50 / 50	9.5 (50)	92	50 / 50	8.8 (50)	85	50 / 50
2	10.3 (50)	50 / 50	9.9 (50)	96	50 / 50	9.8 (50)	95	50 / 50	9.4 (50)	91	50 / 50
3	10.3 (50)	50 / 50	10.0 (50)	97	50 / 50	9.9 (50)	96	50 / 50	9.3 (50)	90	50 / 50
4	10.1 (50)	50 / 50	9.8 (50)	97	50 / 50	9.6 (50)	95	50 / 50	9.2 (50)	91	50 / 50
5	10.2 (50)	50 / 50	10.0 (50)	98	50 / 50	9.8 (50)	96	50 / 50	9.2 (50)	90	50 / 50
6	9.8 (50)	50 / 50	9.6 (49)	98	50 / 50	9.5 (50)	97	50 / 50	8.9 (50)	91	50 / 50
7	9.6 (50)	50 / 50	9.4 (50)	98	50 / 50	9.1 (50)	95	50 / 50	8.9 (50)	93	50 / 50
8	9.6 (50)	50 / 50	9.3 (50)	97	50 / 50	9.1 (50)	95	50 / 50	8.6 (50)	90	50 / 50
9	9.8 (50)	50 / 50	9.5 (50)	97	50 / 50	9.4 (50)	96	50 / 50	8.8 (50)	90	50 / 50
10	9.8 (50)	50 / 50	9.6 (50)	98	50 / 50	9.3 (50)	95	50 / 50	8.7 (50)	89	50 / 50
11	9.8 (50)	50 / 50	9.5 (50)	97	50 / 50	9.2 (50)	94	50 / 50	8.7 (50)	89	50 / 50
12	9.7 (50)	50 / 50	9.5 (50)	98	50 / 50	9.1 (50)	94	50 / 50	8.6 (50)	89	50 / 50
13	10.0 (50)	50 / 50	9.7 (50)	97	50 / 50	9.5 (50)	95	50 / 50	8.8 (50)	88	50 / 50
14	9.8 (50)	50 / 50	9.6 (50)	98	50 / 50	9.1 (50)	93	50 / 50	8.6 (50)	88	50 / 50
18 a)	- (-)	50 / 50	- (-)	-	50 / 50	- (-)	-	50 / 50	- (-)	-	50 / 50
20	9.8 (50)	50 / 50	9.6 (50)	98	50 / 50	9.1 (50)	93	50 / 50	8.7 (50)	89	50 / 50
22	10.4 (50)	50 / 50	9.9 (50)	95	50 / 50	9.6 (50)	92	50 / 50	9.1 (50)	88	50 / 50
26	10.1 (50)	50 / 50	9.9 (50)	98	50 / 50	9.5 (50)	94	50 / 50	8.9 (50)	88	50 / 50
30	10.1 (50)	50 / 50	9.9 (50)	98	50 / 50	9.5 (50)	94	50 / 50	8.9 (49)	88	49 / 50
34	10.1 (50)	50 / 50	9.9 (50)	98	50 / 50	9.4 (50)	93	50 / 50	8.8 (49)	87	49 / 50
38	10.1 (50)	50 / 50	9.7 (50)	96	50 / 50	9.3 (50)	92	50 / 50	8.8 (49)	87	49 / 50
42	10.4 (50)	50 / 50	10.3 (50)	99	50 / 50	9.8 (50)	94	50 / 50	8.9 (48)	86	48 / 50
46	10.4 (49)	49 / 50	10.1 (50)	97	50 / 50	9.8 (50)	94	50 / 50	9.2 (48)	88	48 / 50
50	10.6 (49)	49 / 50	10.3 (50)	97	50 / 50	9.9 (50)	93	50 / 50	9.0 (45)	85	45 / 50
54	10.8 (49)	49 / 50	10.5 (50)	97	50 / 50	10.0 (50)	93	50 / 50	9.3 (44)	86	44 / 50
58	11.0 (49)	49 / 50	10.7 (50)	97	50 / 50	10.1 (50)	92	50 / 50	9.4 (44)	85	44 / 50
62	10.9 (49)	49 / 50	10.5 (50)	96	50 / 50	10.0 (50)	92	50 / 50	9.1 (44)	83	44 / 50
66	10.8 (49)	49 / 50	10.6 (50)	98	50 / 50	10.0 (50)	93	50 / 50	9.2 (44)	85	44 / 50
70	11.4 (49)	49 / 50	10.9 (50)	96	50 / 50	10.3 (50)	90	50 / 50	9.4 (43)	82	43 / 50
74	11.1 (48)	48 / 50	10.6 (50)	95	50 / 50	10.3 (49)	93	49 / 50	9.2 (42)	83	42 / 50
78	11.4 (48)	48 / 50	10.5 (50)	92	50 / 50	10.0 (48)	88	48 / 50	9.6 (40)	84	40 / 50
82	11.2 (47)	47 / 50	10.8 (50)	96	50 / 50	10.3 (48)	92	48 / 50	9.9 (37)	88	37 / 50
86	11.2 (46)	46 / 50	11.0 (50)	98	50 / 50	10.5 (45)	94	45 / 50	9.8 (34)	88	34 / 50
90	11.8 (41)	41 / 50	11.3 (50)	96	50 / 50	10.8 (43)	92	43 / 50	9.7 (32)	82	32 / 50
94	11.5 (40)	40 / 50	10.9 (49)	95	49 / 50	10.4 (43)	90	43 / 50	9.6 (31)	83	31 / 50
98	11.9 (39)	39 / 50	11.5 (47)	97	47 / 50	11.0 (41)	92	41 / 50	9.7 (28)	82	28 / 50
102	11.6 (38)	38 / 50	11.2 (43)	97	43 / 50	10.5 (40)	91	40 / 50	9.9 (25)	85	25 / 50
104	12.0 (38)	38 / 50	11.3 (43)	94	43 / 50	10.7 (40)	89	40 / 50	10.1 (25)	84	25 / 50

< > : No. of effective animals, ( ) : No. of measured animals, Av. FC. : Averaged food consumption (Unit : g).
a) : Food consumption could not be calculated because the measurement of food consumption failed.

TABLE 5 WATER CONSUMPTION CHANGES OF MALE RATS 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	17.7 (50)	50	50 / 50	14.6 (50)	82	50 / 50	13.5 (50)	76	50 / 50	14.2 (50)	80	50 / 50
2	19.2 (50)	50	50 / 50	15.7 (50)	82	50 / 50	14.3 (50)	74	50 / 50	13.4 (50)	70	50 / 50
3	19.0 (50)	50	50 / 50	16.5 (50)	87	50 / 50	15.4 (50)	81	50 / 50	14.2 (50)	75	50 / 50
4	18.0 (50)	50	50 / 50	15.9 (50)	88	50 / 50	14.2 (50)	79	50 / 50	12.9 (46)	72	50 / 50
5	18.8 (50)	50	50 / 50	16.7 (50)	89	50 / 50	15.9 (50)	85	50 / 50	13.9 (50)	74	50 / 50
6	19.1 (50)	50	50 / 50	16.7 (50)	87	50 / 50	15.9 (50)	83	50 / 50	13.7 (50)	72	50 / 50
7	19.5 (50)	50	50 / 50	16.8 (50)	86	50 / 50	15.2 (50)	78	50 / 50	13.1 (50)	67	50 / 50
8	19.1 (50)	50	50 / 50	16.2 (50)	85	50 / 50	14.5 (50)	76	50 / 50	12.2 (50)	64	50 / 50
9	18.7 (50)	50	50 / 50	16.0 (50)	86	50 / 50	13.8 (50)	74	50 / 50	11.8 (50)	63	50 / 50
10	18.5 (50)	50	50 / 50	15.4 (50)	83	50 / 50	13.2 (50)	71	50 / 50	11.0 (50)	59	50 / 50
11	17.8 (50)	50	50 / 50	14.8 (50)	83	50 / 50	13.1 (50)	74	50 / 50	10.8 (50)	61	50 / 50
12	17.1 (50)	50	50 / 50	14.3 (50)	84	50 / 50	12.8 (50)	75	50 / 50	10.2 (50)	60	50 / 50
13	18.7 (50)	50	50 / 50	16.4 (50)	88	50 / 50	13.0 (50)	70	50 / 50	12.4 (50)	66	50 / 50
14	18.5 (50)	50	50 / 50	15.0 (50)	81	50 / 50	12.7 (50)	69	50 / 50	11.4 (50)	62	50 / 50
18	17.0 (50)	50	50 / 50	15.1 (50)	89	50 / 50	11.5 (50)	68	50 / 50	10.1 (50)	59	50 / 50
22	17.5 (50)	50	50 / 50	14.6 (50)	83	50 / 50	12.0 (50)	69	50 / 50	10.4 (50)	59	50 / 50
26	17.0 (50)	50	50 / 50	14.7 (50)	86	50 / 50	12.1 (50)	71	50 / 50	10.8 (50)	64	50 / 50
30	17.0 (50)	50	50 / 50	15.3 (50)	90	50 / 50	12.4 (50)	73	50 / 50	10.6 (49)	62	50 / 50
34	17.8 (49)	50	50 / 50	15.4 (50)	87	50 / 50	12.7 (50)	71	50 / 50	10.5 (49)	59	50 / 50
38	17.0 (50)	50	50 / 50	14.9 (49)	88	49 / 50	12.1 (49)	71	49 / 50	11.1 (50)	65	50 / 50
42	17.9 (50)	50	50 / 50	15.7 (49)	88	49 / 50	13.2 (49)	74	49 / 50	11.4 (49)	64	49 / 50
46	16.9 (50)	50	50 / 50	15.1 (49)	89	49 / 50	12.2 (49)	72	49 / 50	9.6 (47)	57	47 / 50
50	17.2 (50)	50	50 / 50	15.4 (49)	90	49 / 50	12.6 (49)	73	49 / 50	10.5 (46)	61	46 / 50
54	15.4 (50)	50	50 / 50	13.4 (48)	87	48 / 50	11.0 (49)	71	49 / 50	9.4 (46)	61	46 / 50
58	16.7 (50)	50	50 / 50	14.8 (48)	89	48 / 50	12.4 (49)	74	49 / 50	10.3 (46)	62	46 / 50
62	17.8 (50)	50	50 / 50	15.1 (48)	85	48 / 50	12.3 (49)	69	49 / 50	10.0 (45)	56	45 / 50
66	17.2 (50)	50	50 / 50	15.7 (48)	91	48 / 50	12.3 (49)	72	49 / 50	10.5 (44)	61	44 / 50
70	17.1 (48)	48	48 / 50	15.2 (47)	89	47 / 50	12.5 (49)	73	49 / 50	9.9 (44)	58	44 / 50
74	17.4 (47)	47	47 / 50	15.4 (46)	89	46 / 50	13.2 (49)	76	49 / 50	10.8 (44)	62	44 / 50
78	17.8 (46)	46	46 / 50	16.3 (46)	92	46 / 50	14.1 (49)	79	49 / 50	11.6 (44)	65	44 / 50
82	18.0 (45)	45	45 / 50	16.7 (46)	93	46 / 50	14.6 (49)	81	49 / 50	11.6 (44)	64	44 / 50
86	18.4 (45)	45	45 / 50	16.7 (46)	91	46 / 50	13.8 (47)	75	47 / 50	11.7 (44)	64	44 / 50
90	19.7 (44)	44	44 / 50	18.6 (46)	94	46 / 50	14.7 (46)	75	46 / 50	12.3 (43)	62	43 / 50
94	19.0 (42)	42	42 / 50	16.4 (45)	86	45 / 50	14.2 (46)	75	46 / 50	12.5 (42)	66	42 / 50
98	18.9 (40)	40	40 / 50	15.7 (44)	83	44 / 50	13.5 (43)	71	43 / 50	11.3 (42)	60	42 / 50
102	20.2 (39)	39	39 / 50	16.4 (42)	81	42 / 50	14.9 (41)	74	41 / 50	13.0 (41)	64	41 / 50
104	20.4 (38)	38	38 / 50	16.2 (41)	79	41 / 50	14.7 (40)	72	40 / 50	12.0 (39)	59	39 / 50

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

TABLE 6 WATER CONSUMPTION CHANGES OF FEMALE RATS 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	15.9 (50)	50 / 50	12.2 (50)	77	50 / 50	11.2 (49)	70	50 / 50	10.6 (50)	67	50 / 50
2	17.6 (50)	50 / 50	12.4 (50)	70	50 / 50	11.3 (50)	64	50 / 50	10.7 (50)	61	50 / 50
3	16.8 (50)	50 / 50	12.2 (50)	73	50 / 50	11.1 (50)	66	50 / 50	10.1 (50)	60	50 / 50
4	17.9 (49)	50 / 50	12.6 (50)	70	50 / 50	10.9 (50)	61	50 / 50	9.8 (50)	55	50 / 50
5	18.5 (50)	50 / 50	12.3 (50)	66	50 / 50	10.8 (50)	58	50 / 50	9.6 (50)	52	50 / 50
6	17.8 (50)	50 / 50	12.3 (50)	69	50 / 50	10.7 (50)	60	50 / 50	9.9 (50)	56	50 / 50
7	17.9 (47)	50 / 50	12.1 (50)	68	50 / 50	10.2 (50)	57	50 / 50	9.6 (50)	54	50 / 50
8	17.8 (47)	50 / 50	12.4 (50)	70	50 / 50	10.0 (50)	56	50 / 50	8.7 (50)	49	50 / 50
9	17.6 (48)	50 / 50	11.8 (50)	67	50 / 50	10.0 (50)	57	50 / 50	10.1 (50)	57	50 / 50
10	18.6 (46)	50 / 50	12.3 (50)	66	50 / 50	10.1 (50)	54	50 / 50	10.4 (50)	56	50 / 50
11	20.7 (48)	50 / 50	12.0 (50)	58	50 / 50	9.6 (50)	46	50 / 50	9.4 (50)	45	50 / 50
12	17.7 (49)	50 / 50	11.4 (50)	64	50 / 50	9.1 (50)	51	50 / 50	8.5 (50)	48	50 / 50
13	19.3 (44)	50 / 50	12.0 (50)	62	50 / 50	9.9 (50)	51	50 / 50	8.2 (50)	42	50 / 50
14	18.8 (47)	50 / 50	11.8 (50)	63	50 / 50	9.7 (50)	52	50 / 50	8.2 (50)	44	50 / 50
18	16.3 (49)	50 / 50	9.9 (49)	61	50 / 50	7.4 (50)	45	50 / 50	6.3 (50)	39	50 / 50
22	19.9 (47)	50 / 50	12.2 (48)	61	50 / 50	9.9 (50)	50	50 / 50	8.6 (50)	43	50 / 50
26	17.8 (49)	50 / 50	12.2 (50)	69	50 / 50	9.4 (50)	53	50 / 50	8.2 (50)	46	50 / 50
30	18.6 (49)	50 / 50	12.0 (49)	65	50 / 50	9.3 (50)	50	50 / 50	8.2 (49)	44	49 / 50
34	17.6 (49)	50 / 50	12.3 (50)	70	50 / 50	10.2 (50)	58	50 / 50	8.7 (49)	49	49 / 50
38	17.1 (48)	50 / 50	11.6 (50)	68	50 / 50	9.2 (50)	54	50 / 50	8.6 (49)	50	49 / 50
42	17.5 (49)	50 / 50	13.3 (50)	76	50 / 50	10.3 (50)	59	50 / 50	8.8 (48)	50	48 / 50
46	15.7 (48)	49 / 50	10.9 (50)	69	50 / 50	9.8 (50)	62	50 / 50	8.0 (48)	51	48 / 50
50	16.3 (48)	49 / 50	12.5 (50)	77	50 / 50	10.0 (50)	61	50 / 50	8.5 (45)	52	45 / 50
54	15.4 (48)	49 / 50	12.8 (50)	83	50 / 50	10.0 (50)	65	50 / 50	8.5 (44)	55	44 / 50
58	15.0 (47)	49 / 50	11.8 (50)	79	50 / 50	9.9 (50)	66	50 / 50	8.4 (44)	56	44 / 50
62	15.3 (48)	49 / 50	11.3 (50)	74	50 / 50	9.5 (50)	62	50 / 50	8.1 (44)	53	44 / 50
66	16.1 (49)	49 / 50	11.2 (50)	70	50 / 50	9.8 (50)	61	50 / 50	8.8 (44)	55	44 / 50
70	15.7 (48)	49 / 50	11.3 (50)	72	50 / 50	10.0 (50)	64	50 / 50	9.2 (43)	59	43 / 50
74	14.7 (48)	48 / 50	11.6 (50)	79	50 / 50	10.7 (49)	73	49 / 50	9.2 (42)	63	42 / 50
78	15.2 (48)	48 / 50	11.4 (50)	75	50 / 50	10.7 (48)	70	48 / 50	10.2 (40)	67	40 / 50
82	15.3 (46)	47 / 50	12.0 (50)	78	50 / 50	11.4 (48)	75	48 / 50	11.2 (37)	73	37 / 50
86	14.9 (46)	46 / 50	12.0 (50)	81	50 / 50	11.6 (45)	78	45 / 50	10.9 (34)	73	34 / 50
90	16.2 (41)	41 / 50	13.1 (50)	81	50 / 50	12.3 (43)	76	43 / 50	11.5 (32)	71	32 / 50
94	17.0 (40)	40 / 50	12.3 (49)	72	49 / 50	11.7 (43)	69	43 / 50	11.6 (31)	68	31 / 50
98	16.8 (39)	39 / 50	12.8 (47)	76	47 / 50	13.0 (41)	77	41 / 50	12.6 (28)	75	28 / 50
102	15.9 (38)	38 / 50	13.4 (43)	84	43 / 50	13.6 (40)	86	40 / 50	12.3 (25)	77	25 / 50
104	17.2 (36)	38 / 50	14.0 (43)	81	43 / 50	14.1 (40)	82	40 / 50	12.9 (25)	75	25 / 50

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

TABLE 7 HEMATOLOGY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals	38	39	40	38
HEMOGLOBIN (g/dL)	14.4 ± 1.7	14.2 ± 2.4	14.3 ± 2.7	15.2 ± 1.8 *
PLATELET ($10^3/\mu$ L)	848 ± 266	820 ± 264	799 ± 308	705 ± 139 **

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

TABLE 8 HEMATOLOGY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals	38	43	40	24
RED BLOOD CELL ($10^6/\mu$ L)	8.19 ± 0.59	7.73 ± 1.13 *	7.86 ± 1.22 **	7.80 ± 0.56 **
HEMOGLOBIN (g/dL)	14.9 ± 1.1	14.2 ± 1.9 *	14.5 ± 2.1 *	14.2 ± 0.8 **
HEMATOCRIT (%)	43.1 ± 2.7	41.1 ± 4.8	42.0 ± 6.4 *	41.4 ± 2.2 **
PLATELET ($10^3/\mu$ L)	634 ± 144	612 ± 136	674 ± 166	679 ± 82 *

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

TABLE 9 BIOCHEMISTRY OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm		20000 ppm	
No. of examined animals	38	41	40		38	
TOTAL PROTEIN (g/dL)	6.7 ± 0.5	6.6 ± 0.4	6.6 ± 0.3		6.5 ± 0.4	**
A/G RATIO	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	*	0.9 ± 0.1	**
T-CHOLESTEROL (mg/dL)	181 ± 53	160 ± 38	151 ± 39	**	145 ± 41	**
TRIGLYCERIDE (mg/dL)	82 ± 51	74 ± 48	71 ± 43		50 ± 35	**
PHOSPHOLIPID (mg/dL)	255 ± 75	234 ± 81	219 ± 54	*	209 ± 60	**
LDH (IU/L)	188 ± 75	554 ± 2138	218 ± 351		156 ± 78	**
ALP (IU/L)	203 ± 58	265 ± 266	264 ± 106	**	225 ± 60	
POTASSIUM (mEq/L)	3.4 ± 0.2	3.6 ± 0.5	3.6 ± 0.3	*	3.5 ± 0.3	*

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

TABLE 10 BIOCHEMISTRY OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm		20000 ppm	
No. of examined animals	38	43	40		24	
TOTAL PROTEIN (g/dL)	6.9 ± 0.4	6.9 ± 0.5	6.8 ± 0.5		6.4 ± 0.5	**
A/G RATIO	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.2		1.1 ± 0.1	*
AST (IU/L)	161 ± 112	197 ± 208	120 ± 63		109 ± 95	**
ALT (IU/L)	70 ± 44	65 ± 38	46 ± 15	*	44 ± 23	**
LDH (IU/L)	215 ± 62	378 ± 618	238 ± 147		176 ± 79	*
UREA NITROGEN (mg/dL)	16.7 ± 1.8	16.4 ± 1.7	17.9 ± 3.3		18.4 ± 3.2	*
INORGANIC PHOSPHORUS (mg/dL)	3.8 ± 0.7	4.1 ± 0.7	4.3 ± 0.6	**	4.4 ± 0.7	**

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

TABLE 11 URINALYSIS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name		Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals		38	41	40	39
	Grade				
pH	5.0	0	0	0	0
	6.0	1	2	0	1
	6.5	5	11	4	18
	7.0	18	18	14	7
	7.5	11	8	12	11
	8.0	3	2	9	2
	8.5	0	0	1	0
	Chi square test				*
Protein	−	0	0	0	0
	±	0	0	0	0
	+	0	1	1	1
	2+	12	3	6	7
	3+	22	30	26	27
	4+	4	7	7	4
	Chi square test		*		
Ketone body	−	34	29	32	26
	±	4	11	6	13
	+	0	1	2	0
	2+	0	0	0	0
	3+	0	0	0	0
	4+	0	0	0	0
	Chi square test				*

Significant difference: * : $p \leqq 0.05$ ** : $p \leqq 0.01$

TABLE 12 URINALYSIS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name		Control	2000 ppm	6325 ppm	20000 ppm
No. of examined animals		38	43	40	25
	Grade				
pH	5.0	0	0	0	0
	6.0	0	0	1	6
	6.5	2	7	13	8
	7.0	5	8	11	4
	7.5	7	12	6	3
	8.0	20	15	6	3
	8.5	4	1	3	1
	Chi square test			**	**
Protein	−	0	0	0	0
	±	1	0	1	0
	+	15	4	0	1
	2+	11	16	15	3
	3+	7	18	17	14
	4+	4	5	7	7
	Chi square test		*	**	**
Occult blood	−	36	37	19	1
	±	0	1	1	0
	+	1	0	1	0
	2+	0	1	1	0
	3+	1	4	18	24
	Chi square test			**	**

Significant difference: * : $p \leqq 0.05$ ** : $p \leqq 0.01$

TABLE 13 ORGAN WEIGHTS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm		6325 ppm		20000 ppm	
No. of examined animals	38	41		40		39	
Body weight (g)	388 ± 32	366 ± 35		349 ± 20	**	319 ± 31	**
Adrenals (g)	0.069 ± 0.010	0.094 ± 0.184		0.064 ± 0.018	**	0.061 ± 0.024	**
Adrenals (%)	0.018 ± 0.002	0.027 ± 0.054		0.018 ± 0.005		0.019 ± 0.008	
Heart (g)	1.193 ± 0.098	1.159 ± 0.083		1.135 ± 0.118	*	1.044 ± 0.086	**
Heart (%)	0.309 ± 0.026	0.319 ± 0.031		0.326 ± 0.036	*	0.329 ± 0.031	*
Lungs (g)	1.350 ± 0.073	1.473 ± 0.405		1.349 ± 0.210		1.238 ± 0.112	**
Lungs (%)	0.350 ± 0.027	0.412 ± 0.163	**	0.389 ± 0.072	**	0.391 ± 0.047	**
Kidneys (g)	2.571 ± 0.225	2.653 ± 0.298		2.497 ± 0.127		2.407 ± 0.217	**
Kidneys (%)	0.665 ± 0.060	0.735 ± 0.146	**	0.718 ± 0.045	**	0.759 ± 0.085	**
Spleen (g)	0.995 ± 0.435	1.193 ± 1.345		1.210 ± 1.357		0.818 ± 0.537	**
Spleen (%)	0.257 ± 0.113	0.336 ± 0.431		0.355 ± 0.434		0.257 ± 0.181	
Liver (g)	10.396 ± 1.253	10.038 ± 1.383		9.514 ± 0.957	*	8.405 ± 0.949	**
Liver (%)	2.682 ± 0.232	2.751 ± 0.353		2.737 ± 0.316		2.640 ± 0.238	
Brain (g)	2.053 ± 0.043	2.057 ± 0.049		2.049 ± 0.038		2.029 ± 0.045	*
Brain (%)	0.533 ± 0.044	0.568 ± 0.062		0.590 ± 0.037	**	0.643 ± 0.081	**

Mean ± S.D.
Significant difference: * : $p \leqq 0.05$ ** : $p \leqq 0.01$ Test of Dunnett

TABLE 14 ORGAN WEIGHTS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm		6325 ppm		20000 ppm	
No. of examined animals	38	43		40		25	
Body weight (g)	250 ± 21	240 ± 24		223 ± 21	**	191 ± 19	**
Adrenals (g)	0.066 ± 0.008	0.147 ± 0.507		0.065 ± 0.015		0.067 ± 0.033	**
Adrenals (%)	0.027 ± 0.004	0.063 ± 0.218		0.030 ± 0.008	*	0.035 ± 0.016	**
Ovaries (g)	0.114 ± 0.023	0.142 ± 0.188		0.347 ± 1.511		0.106 ± 0.021	
Ovaries (%)	0.046 ± 0.011	0.057 ± 0.060		0.158 ± 0.690	**	0.056 ± 0.014	**
Heart (g)	0.855 ± 0.057	0.840 ± 0.056		0.813 ± 0.079	**	0.783 ± 0.104	**
Heart (%)	0.344 ± 0.027	0.353 ± 0.038		0.367 ± 0.039	*	0.416 ± 0.094	**
Lungs (g)	0.995 ± 0.065	1.015 ± 0.183		1.024 ± 0.304	*	0.944 ± 0.117	**
Lungs (%)	0.401 ± 0.039	0.427 ± 0.084		0.462 ± 0.139	**	0.502 ± 0.104	**
Kidneys (g)	1.709 ± 0.135	1.739 ± 0.146		1.793 ± 0.238		1.707 ± 0.156	
Kidneys (%)	0.687 ± 0.056	0.729 ± 0.070	*	0.807 ± 0.085	**	0.901 ± 0.105	**
Spleen (g)	0.573 ± 0.176	1.013 ± 1.458		0.717 ± 0.732		0.523 ± 0.394	**
Spleen (%)	0.231 ± 0.072	0.426 ± 0.599		0.320 ± 0.310		0.287 ± 0.278	
Liver (g)	6.480 ± 0.809	6.571 ± 1.491		6.062 ± 1.059	*	5.508 ± 0.845	**
Liver (%)	2.605 ± 0.324	2.736 ± 0.523		2.717 ± 0.326		2.900 ± 0.417	**
Brain (g)	1.894 ± 0.039	1.880 ± 0.038		1.863 ± 0.038	**	1.840 ± 0.048	**
Brain (%)	0.764 ± 0.069	0.792 ± 0.087		0.843 ± 0.073	**	0.975 ± 0.110	**

Mean ± S.D.
Significant difference: * : $p \leqq 0.05$ ** : $p \leqq 0.01$ Test of Dunnett

TABLE 15 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm	Peto test	Cochran-Armitage test
Number of examined animals	50	50	50	50		
thyroid	<50>	<50>	<50>	<50>		
C-cell adenoma	12 (24 %)	6 (12 %)	14 (28 %)	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 16 INCIDENCES OF SELECTED NEOPLASTIC LESIONS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2000 ppm	6325 ppm	20000 ppm	Peto test	Cochran-Armitage test
Number of examined animals	50	50	50	50		
spleen	<50>	<50>	<50>	<50>		
mononuclear cell leukemia	3 (6 %)	5 (10 %)	7 (14 %)	6 (12 %)	↑	
uterus	<50>	<50>	<50>	<50>		
endometrial stromal polyp	10 (20 %)	7 (14 %)	5 (10 %)	12 (24 %)	↑	

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 17 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control				2000 ppm				6325 ppm				20000 ppm			
Number of examined animals	50				50				50				50			
Grade of non-neoplastic lesion	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
liver	<50>				<50>				<50>				<50>			
acidophilic cell focus	11	1	1	0	8	2	0	0	9	0	2	0	2	0	0	0 *
kidney	<50>				<50>				<50>				<50>			
chronic nephropathy	27	11	3	0	33	12	1	0	47	0	0	0 **	38	3	0	0 *
papillary necrosis	0	1	0	0	1	2	0	0	1	0	0	0	10	1	0	0 **
thyroid	<50>				<50>				<50>				<50>			
C-cell hyperplasia	16	0	0	0	16	0	0	0	9	0	0	0	5	0	0	0 *
eye	<50>				<50>				<50>				<50>			
retinal atrophy	24	21	4	0	23	13	9	0	28	9	8	0 *	34	8	6	0 *

Grade 1: Slight 2 : Moderate 3 : Marked 4 :Severe
< > : Number of animals examined at the site
Significant difference ; * : $p \leqq 0.05$ ** : $p \leqq 0.01$ Test of Chi Square

TABLE 18 INCIDENCES OF SELECTED NON-NEOPLASTIC LESIONS OF FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control				2000 ppm				6325 ppm				20000 ppm			
Number of examined animals	50				50				50				50			
Grade of non-neoplastic lesion	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
nasal cavity	<50>				<50>				<50>				<50>			
mineralization	17	0	0	0	17	0	0	0	17	0	0	0	7	0	0	0 *
liver	<50>				<50>				<50>				<50>			
granulation	31	4	0	0	21	5	0	0	17	1	0	0 **	19	2	0	0 *
kidney	<50>				<50>				<50>				<50>			
papillary necrosis	0	0	0	0	19	1	0	0 **	18	11	0	0 **	21	19	0	0 **
mineralization:papilla	0	0	0	0	0	0	0	0	3	8	0	0 **	4	15	0	0 **
urothelial hyperplasia:pelvis	0	0	0	0	0	0	0	0	2	2	1	0	5	3	0	0 *
eye	<50>				<50>				<50>				<50>			
retinal atrophy	11	35	3	0	20	28	2	0	37	10	0	0 **	32	11	6	0 **
adrenal	<50>				<50>				<50>				<50>			
peliosis-like lesion	33	3	0	0	36	5	0	0	32	5	0	0	23	1	0	0 *
nasolacrimal duct	<50>				<50>				<50>				<50>			
inflammation	7	2	0	0	2	1	0	0	3	1	0	0	1	0	0	0 *

Grade 1: Slight 2 : Moderate 3 : Marked 4 :Severe
< > : Number of animals examined at the site
Significant difference ; * : $p \leqq 0.05$ ** : $p \leqq 0.01$ Test of Chi Square

TABLE 19 HISTORICAL CONTROL DATA OF SELECTED NEOPLASTIC LESIONS IN JAPAN BIOASSAY RESEARCH CENTER : F344/DuCrj FEMALE RATS

Organs Tumors	No. of animals examined	No. of animals bearing tumor	Incidence (%)	Min. - Max. (%)
Uterus	1696			
Endometrial stromal polyp		246	14.5	2 - 28
Spleen	1697			
Mononuclear cell leukemia		222	13.1	2 - 26

34 carcinogenicity studies examined in Japan Bioassay Research Center were used.
Study No. : 0043, 0059, 0061, 0063, 0065, 0067, 0095, 0104, 0115, 0130, 0141, 0158, 0162, 0189, 0205, 0210, 0224, 0242, 0267, 0269, 0278, 0284, 0296, 0303, 0318, 0328, 0342, 0347, 0365, 0371, 0399, 0401, 0417, 0421

TABLE 20 CAUSE OF DEATH OF RATS 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		12	9	10	11	12	7	10	25
No microscopical confirmation		0	0	0	2	0	0	1	2
Urinary system lesion		0	1	0	0	0	0	0	0
Renal lesion		0	1	1	1	0	0	0	8
Urinary retention		1	1	0	0	0	0	0	0
Deglutition disorder		0	0	0	2	0	0	1	2
Tumor death ：	leukemia	1	2	3	1	2	1	4	5
	skin/appendage	0	0	1	0	0	0	0	0
	subcutis	1	1	1	1	0	0	0	1
	nasal cavity	0	0	0	0	0	1	0	0
	oral cavity	0	0	0	0	1	0	1	0
	tooth	0	1	0	0	0	0	1	0
	large intestine	0	0	0	0	0	1	0	1
	liver	0	0	0	1	0	0	0	0
	pituitary gland	3	0	1	2	3	1	1	2
	thyroid	1	0	0	0	0	0	0	0
	adrenal gland	0	1	1	0	0	1	0	0
	uterus	—	—	—	—	2	0	0	1
	mammary gland	0	0	0	0	1	2	0	2
	preputial/clitoral gland	2	0	0	0	0	0	0	1
	brain	2	0	0	0	0	0	1	0
	spinal cord	1	0	0	0	0	0	0	0
	muscle	0	0	1	0	0	0	0	0
	bone	0	0	1	0	2	0	0	0
	vertebra	0	0	0	1	0	0	0	0
	mediastinum	0	0	0	0	1	0	0	0
	retroperitoneum	0	1	0	0	0	0	0	0