アセト酢酸メチルのラットを用いた経口投与による
１３週間毒性試験（混水試験）報告書

試験番号：　０４２６

TABLES

TABLES

TABLE 1 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Wt. <10>	No. of Surviv.	Av. Wt. <10>	% of cont.	No. of Surviv.	Av. Wt. <10>	% of cont.	No. of Surviv.	Av. Wt. <10>	% of cont.	No. of Surviv.	Av. Wt. <10>	% of cont.	No. of Surviv.	Av. Wt. <10>	% of cont.	No. of Surviv.
0	127 (10)	10 / 10	127 (10)	100	10 / 10	127 (10)	100	10 / 10	127 (10)	100	10 / 10	127 (10)	100	10 / 10	127 (10)	100	10 / 10
1	159 (10)	10 / 10	156 (10)	98	10 / 10	154 (10)	97	10 / 10	154 (10)	97	10 / 10	148 (10)	93	10 / 10	107 (10)	67	10 / 10
2	190 (10)	10 / 10	185 (10)	97	10 / 10	183 (10)	96	10 / 10	185 (10)	97	10 / 10	180 (10)	95	10 / 10	144 (10)	76	10 / 10
3	216 (10)	10 / 10	209 (10)	97	10 / 10	209 (10)	97	10 / 10	210 (10)	97	10 / 10	204 (10)	94	10 / 10	177 (10)	82	10 / 10
4	237 (10)	10 / 10	229 (10)	97	10 / 10	228 (10)	96	10 / 10	229 (10)	97	10 / 10	225 (10)	95	10 / 10	200 (10)	84	10 / 10
5	251 (10)	10 / 10	244 (10)	97	10 / 10	242 (10)	96	10 / 10	242 (10)	96	10 / 10	238 (10)	95	10 / 10	216 (10)	86	10 / 10
6	261 (10)	10 / 10	254 (10)	97	10 / 10	249 (10)	95	10 / 10	250 (10)	96	10 / 10	243 (10)	93	10 / 10	221 (10)	85	10 / 10
7	277 (10)	10 / 10	270 (10)	97	10 / 10	264 (10)	95	10 / 10	263 (10)	95	10 / 10	258 (10)	93	10 / 10	235 (10)	85	10 / 10
8	290 (10)	10 / 10	281 (10)	97	10 / 10	274 (10)	94	10 / 10	274 (10)	94	10 / 10	267 (10)	92	10 / 10	245 (10)	84	10 / 10
9	300 (10)	10 / 10	288 (10)	96	10 / 10	282 (10)	94	10 / 10	281 (10)	94	10 / 10	273 (10)	91	10 / 10	250 (10)	83	10 / 10
10	310 (10)	10 / 10	297 (10)	96	10 / 10	288 (10)	93	10 / 10	286 (10)	92	10 / 10	280 (10)	90	10 / 10	253 (10)	82	10 / 10
11	315 (10)	10 / 10	302 (10)	96	10 / 10	292 (10)	93	10 / 10	290 (10)	92	10 / 10	281 (10)	89	10 / 10	256 (10)	81	10 / 10
12	323 (10)	10 / 10	308 (10)	95	10 / 10	296 (10)	92	10 / 10	297 (10)	92	10 / 10	285 (10)	88	10 / 10	264 (10)	82	10 / 10
13	326 (10)	10 / 10	310 (10)	95	10 / 10	299 (10)	92	10 / 10	299 (10)	92	10 / 10	287 (10)	88	10 / 10	264 (10)	81	10 / 10

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

TABLE 2 SURVIVAL ANIMAL NUMBERS AND BODY WEIGHT CHANGES OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Wt.	No. of Surviv.	Av. Wt.	% of cont.	No. of Surviv.	Av. Wt.	% of cont.	No. of Surviv.	Av. Wt.	% of cont.	No. of Surviv.	Av. Wt.	% of cont.	No. of Surviv.	Av. Wt.	% of cont.	No. of Surviv.
	<10>		<10>			<10>			<10>			<10>			<10>		
0	100 (10)	10 / 10	100 (10)	100	10 / 10	100 (10)	100	10 / 10	100 (10)	100	10 / 10	100 (10)	100	10 / 10	100 (10)	100	10 / 10
1	113 (10)	10 / 10	115 (10)	102	10 / 10	114 (10)	101	10 / 10	112 (10)	99	10 / 10	110 (10)	97	10 / 10	91 (10)	81	9 / 10
2	123 (10)	10 / 10	126 (10)	102	10 / 10	126 (10)	102	10 / 10	124 (10)	101	10 / 10	121 (10)	98	10 / 10	114 (9)	93	9 / 10
3	132 (10)	10 / 10	135 (10)	102	10 / 10	135 (10)	102	10 / 10	132 (10)	100	10 / 10	131 (10)	99	10 / 10	128 (9)	97	9 / 10
4	140 (10)	10 / 10	142 (10)	101	10 / 10	142 (10)	101	10 / 10	141 (10)	101	10 / 10	137 (10)	98	10 / 10	136 (9)	97	9 / 10
5	147 (10)	10 / 10	149 (10)	101	10 / 10	147 (10)	100	10 / 10	147 (10)	100	10 / 10	141 (10)	96	10 / 10	139 (9)	95	9 / 10
6	150 (10)	10 / 10	150 (10)	100	10 / 10	149 (10)	99	10 / 10	147 (10)	98	10 / 10	141 (10)	94	10 / 10	139 (9)	93	9 / 10
7	156 (10)	10 / 10	157 (10)	101	10 / 10	156 (10)	100	10 / 10	155 (10)	99	10 / 10	147 (10)	94	10 / 10	145 (9)	93	9 / 10
8	160 (10)	10 / 10	160 (10)	100	10 / 10	159 (10)	99	10 / 10	158 (10)	99	10 / 10	150 (10)	94	10 / 10	147 (9)	92	9 / 10
9	162 (10)	10 / 10	163 (10)	101	10 / 10	162 (10)	100	10 / 10	162 (10)	100	10 / 10	153 (10)	94	10 / 10	151 (9)	93	9 / 10
10	166 (10)	10 / 10	166 (10)	100	10 / 10	165 (10)	99	10 / 10	165 (10)	99	10 / 10	156 (10)	94	10 / 10	153 (9)	92	9 / 10
11	167 (10)	10 / 10	169 (10)	101	10 / 10	165 (10)	99	10 / 10	166 (10)	99	10 / 10	158 (10)	95	10 / 10	154 (9)	92	9 / 10
12	166 (10)	10 / 10	170 (10)	102	10 / 10	168 (10)	101	10 / 10	170 (10)	102	10 / 10	160 (10)	96	10 / 10	158 (9)	95	9 / 10
13	170 (10)	10 / 10	171 (10)	101	10 / 10	170 (10)	100	10 / 10	170 (10)	100	10 / 10	160 (10)	94	10 / 10	160 (9)	94	9 / 10

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

TABLE 3 WATER CONSUMPTION CHANGES OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Wc. <10>	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.
1	17.6 (10)	10 / 10	14.5 (10)	82	10 / 10	13.2 (10)	75	10 / 10	13.4 (10)	76	10 / 10	13.0 (10)	74	10 / 10	6.4 (10)	36	10 / 10
2	18.7 (10)	10 / 10	15.4 (10)	82	10 / 10	14.7 (10)	79	10 / 10	14.5 (10)	78	10 / 10	13.7 (10)	73	10 / 10	11.9 (10)	64	10 / 10
3	19.6 (10)	10 / 10	16.0 (10)	82	10 / 10	15.4 (10)	79	10 / 10	14.8 (10)	76	10 / 10	13.9 (10)	71	10 / 10	12.6 (10)	64	10 / 10
4	19.3 (10)	10 / 10	15.6 (10)	81	10 / 10	14.8 (10)	77	10 / 10	14.2 (10)	74	10 / 10	13.1 (10)	68	10 / 10	12.1 (10)	63	10 / 10
5	18.6 (10)	10 / 10	15.2 (10)	82	10 / 10	14.1 (10)	76	10 / 10	13.4 (10)	72	10 / 10	12.6 (10)	68	10 / 10	11.3 (10)	61	10 / 10
6	17.0 (10)	10 / 10	14.1 (10)	83	10 / 10	12.3 (10)	72	10 / 10	11.9 (10)	70	10 / 10	10.6 (10)	62	10 / 10	9.5 (10)	56	10 / 10
7	18.4 (10)	10 / 10	15.5 (10)	84	10 / 10	13.5 (10)	73	10 / 10	12.8 (10)	70	10 / 10	11.9 (10)	65	10 / 10	10.4 (10)	57	10 / 10
8	18.6 (10)	10 / 10	14.9 (10)	80	10 / 10	13.3 (10)	72	10 / 10	13.0 (10)	70	10 / 10	11.8 (10)	63	10 / 10	10.4 (10)	56	10 / 10
9	18.1 (10)	10 / 10	14.3 (10)	79	10 / 10	13.6 (10)	75	10 / 10	12.9 (10)	71	10 / 10	11.8 (10)	65	10 / 10	10.1 (10)	56	10 / 10
10	17.9 (10)	10 / 10	14.4 (10)	80	10 / 10	13.3 (10)	74	10 / 10	12.6 (10)	70	10 / 10	12.0 (10)	67	10 / 10	10.0 (10)	56	10 / 10
11	17.3 (10)	10 / 10	14.7 (10)	85	10 / 10	12.7 (10)	73	10 / 10	11.4 (10)	66	10 / 10	11.0 (10)	64	10 / 10	9.8 (10)	57	10 / 10
12	16.9 (10)	10 / 10	14.1 (10)	83	10 / 10	11.9 (10)	70	10 / 10	11.8 (10)	70	10 / 10	10.6 (10)	63	10 / 10	10.1 (10)	60	10 / 10
13	18.2 (10)	10 / 10	13.5 (10)	74	10 / 10	12.1 (10)	66	10 / 10	11.3 (10)	62	10 / 10	12.8 (10)	70	10 / 10	9.6 (10)	53	10 / 10

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

TABLE 4 WATER CONSUMPTION CHANGES OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Wc. <10>	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.	Av. Wc. <10>	% of cont.	No. of Surviv.
1	16.4 (10)	10 / 10	11.7 (10)	71	10 / 10	10.6 (10)	65	10 / 10	10.4 (10)	63	10 / 10	9.6 (10)	59	10 / 10	7.5 (10)	46	9 / 10
2	15.3 (10)	10 / 10	11.5 (10)	75	10 / 10	10.7 (10)	70	10 / 10	10.4 (10)	68	10 / 10	9.8 (10)	64	10 / 10	10.3 (9)	67	9 / 10
3	15.7 (10)	10 / 10	11.5 (10)	73	10 / 10	10.6 (10)	68	10 / 10	10.2 (10)	65	10 / 10	9.8 (10)	62	10 / 10	10.7 (9)	68	9 / 10
4	17.4 (9)	10 / 10	11.2 (10)	64	10 / 10	10.3 (10)	59	10 / 10	10.3 (10)	59	10 / 10	9.2 (10)	53	10 / 10	9.8 (9)	56	9 / 10
5	15.5 (9)	10 / 10	11.2 (10)	72	10 / 10	9.7 (10)	63	10 / 10	9.5 (10)	61	10 / 10	10.8 (10)	70	10 / 10	8.0 (9)	52	9 / 10
6	15.1 (9)	10 / 10	9.9 (10)	66	10 / 10	8.9 (10)	59	10 / 10	7.9 (10)	52	10 / 10	7.8 (10)	52	10 / 10	6.8 (9)	45	9 / 10
7	15.8 (8)	10 / 10	11.3 (10)	72	10 / 10	9.9 (10)	63	10 / 10	9.0 (10)	57	10 / 10	8.1 (10)	51	10 / 10	7.8 (9)	49	9 / 10
8	16.9 (9)	10 / 10	11.7 (10)	69	10 / 10	9.8 (10)	58	10 / 10	8.8 (10)	52	10 / 10	8.2 (10)	49	10 / 10	7.6 (9)	45	9 / 10
9	19.1 (8)	10 / 10	11.0 (10)	58	10 / 10	10.2 (10)	53	10 / 10	8.5 (10)	45	10 / 10	7.6 (10)	40	10 / 10	7.2 (9)	38	9 / 10
10	14.8 (7)	10 / 10	10.8 (10)	73	10 / 10	9.8 (10)	66	10 / 10	8.7 (10)	59	10 / 10	7.9 (10)	53	10 / 10	6.7 (9)	45	9 / 10
11	21.5 (10)	10 / 10	11.5 (10)	53	10 / 10	9.4 (10)	44	10 / 10	8.6 (10)	40	10 / 10	7.0 (10)	33	10 / 10	6.6 (9)	31	9 / 10
12	17.1 (9)	10 / 10	11.0 (10)	64	10 / 10	10.0 (10)	58	10 / 10	8.5 (10)	50	10 / 10	7.4 (10)	43	10 / 10	6.8 (9)	40	9 / 10
13	23.5 (10)	10 / 10	11.8 (10)	50	10 / 10	9.5 (10)	40	10 / 10	8.4 (10)	36	10 / 10	7.0 (10)	30	10 / 10	7.1 (9)	30	9 / 10

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

TABLE 5 FOOD CONSUMPTION CHANGES OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Fc. <10>	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.
1	14.2 (10)	10 / 10	13.4 (10)	94	10 / 10	12.8 (10)	90	10 / 10	12.7 (10)	89	10 / 10	11.5 (10)	81	10 / 10	5.8 (10)	41	10 / 10
2	15.7 (10)	10 / 10	14.9 (10)	95	10 / 10	14.2 (10)	90	10 / 10	14.4 (10)	92	10 / 10	13.9 (10)	89	10 / 10	12.0 (10)	76	10 / 10
3	15.8 (10)	10 / 10	15.3 (10)	97	10 / 10	14.8 (10)	94	10 / 10	14.8 (10)	94	10 / 10	14.3 (10)	91	10 / 10	13.2 (10)	84	10 / 10
4	16.5 (10)	10 / 10	15.7 (10)	95	10 / 10	15.2 (10)	92	10 / 10	14.8 (10)	90	10 / 10	14.7 (10)	89	10 / 10	13.9 (10)	84	10 / 10
5	15.8 (10)	10 / 10	15.2 (10)	96	10 / 10	14.8 (10)	94	10 / 10	14.3 (10)	91	10 / 10	14.0 (10)	89	10 / 10	13.6 (10)	86	10 / 10
6	15.4 (10)	10 / 10	14.5 (10)	94	10 / 10	14.3 (10)	93	10 / 10	13.9 (10)	90	10 / 10	13.3 (10)	86	10 / 10	12.6 (10)	82	10 / 10
7	15.9 (10)	10 / 10	15.4 (10)	97	10 / 10	14.7 (10)	92	10 / 10	14.6 (10)	92	10 / 10	13.9 (10)	87	10 / 10	12.7 (10)	80	10 / 10
8	15.5 (10)	10 / 10	14.8 (10)	95	10 / 10	13.9 (10)	90	10 / 10	14.0 (10)	90	10 / 10	13.1 (10)	85	10 / 10	12.0 (10)	77	10 / 10
9	15.1 (10)	10 / 10	14.6 (10)	97	10 / 10	14.1 (10)	93	10 / 10	14.0 (10)	93	10 / 10	13.1 (10)	87	10 / 10	12.2 (10)	81	10 / 10
10	15.2 (10)	10 / 10	14.5 (10)	95	10 / 10	14.1 (10)	93	10 / 10	13.7 (10)	90	10 / 10	13.1 (10)	86	10 / 10	11.9 (10)	78	10 / 10
11	15.2 (10)	10 / 10	14.3 (10)	94	10 / 10	13.8 (10)	91	10 / 10	13.5 (10)	89	10 / 10	12.7 (10)	84	10 / 10	12.0 (10)	79	10 / 10
12	15.0 (10)	10 / 10	13.7 (10)	91	10 / 10	13.1 (10)	87	10 / 10	13.2 (10)	88	10 / 10	12.3 (10)	82	10 / 10	12.1 (10)	81	10 / 10
13	15.7 (10)	10 / 10	14.3 (10)	91	10 / 10	13.4 (10)	85	10 / 10	13.4 (10)	85	10 / 10	13.0 (10)	83	10 / 10	12.3 (10)	78	10 / 10

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

TABLE 6 FOOD CONSUMPTION CHANGES OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Week on Study	Control		2500 ppm			5000 ppm			10000 ppm			20000 ppm			40000 ppm		
	Av. Fc. <10>	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.	Av. Fc. <10>	% of cont.	No. of Surviv.
1	10.4 (10)	10 / 10	10.5 (10)	101	10 / 10	10.1 (10)	97	10 / 10	10.1 (10)	97	10 / 10	9.2 (10)	88	10 / 10	5.8 (10)	56	9 / 10
2	10.4 (10)	10 / 10	10.5 (10)	101	10 / 10	10.2 (10)	98	10 / 10	10.2 (10)	98	10 / 10	9.5 (10)	91	10 / 10	9.6 (9)	92	9 / 10
3	10.7 (10)	10 / 10	10.6 (10)	99	10 / 10	10.2 (10)	95	10 / 10	10.1 (10)	94	10 / 10	9.6 (10)	90	10 / 10	9.8 (9)	92	9 / 10
4	10.4 (10)	10 / 10	10.2 (10)	98	10 / 10	10.1 (10)	97	10 / 10	9.9 (10)	95	10 / 10	9.5 (10)	91	10 / 10	9.5 (9)	91	9 / 10
5	10.7 (10)	10 / 10	10.4 (10)	97	10 / 10	9.9 (10)	93	10 / 10	10.0 (10)	93	10 / 10	9.2 (10)	86	10 / 10	9.0 (9)	84	9 / 10
6	10.1 (10)	10 / 10	9.7 (10)	96	10 / 10	9.4 (10)	93	10 / 10	9.2 (10)	91	10 / 10	9.0 (10)	89	10 / 10	8.6 (9)	85	9 / 10
7	10.3 (10)	10 / 10	10.0 (10)	97	10 / 10	9.7 (10)	94	10 / 10	9.6 (10)	93	10 / 10	9.0 (10)	87	10 / 10	8.6 (9)	83	9 / 10
8	9.8 (10)	10 / 10	9.5 (10)	97	10 / 10	9.3 (10)	95	10 / 10	9.1 (10)	93	10 / 10	8.7 (10)	89	10 / 10	8.5 (9)	87	9 / 10
9	9.6 (10)	10 / 10	9.2 (10)	96	10 / 10	9.1 (10)	95	10 / 10	9.0 (10)	94	10 / 10	8.5 (10)	89	10 / 10	8.2 (9)	85	9 / 10
10	9.7 (10)	10 / 10	9.4 (10)	97	10 / 10	9.1 (10)	94	10 / 10	9.1 (10)	94	10 / 10	8.4 (10)	87	10 / 10	8.0 (9)	82	9 / 10
11	9.8 (10)	10 / 10	9.4 (10)	96	10 / 10	9.0 (10)	92	10 / 10	9.0 (10)	92	10 / 10	8.7 (10)	89	10 / 10	8.2 (9)	84	9 / 10
12	9.5 (10)	10 / 10	9.3 (10)	98	10 / 10	9.0 (10)	95	10 / 10	8.9 (10)	94	10 / 10	8.4 (10)	88	10 / 10	8.1 (9)	85	9 / 10
13	9.8 (10)	10 / 10	9.5 (10)	97	10 / 10	9.1 (10)	93	10 / 10	8.9 (10)	91	10 / 10	8.5 (10)	87	10 / 10	8.2 (9)	84	9 / 10

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

TABLE 7 HEMATOLOGY OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	10	10	9	10	10	9
Red blood cell ($10^6/\mu$ L)	9.47 ± 0.12	9.43 ± 0.26	9.21 ± 0.36	9.27 ± 0.25	9.13 ± 0.19 **	9.15 ± 0.16 **
Hemoglobin (g/dL)	16.1 ± 0.2	16.1 ± 0.4	15.8 ± 0.6	15.9 ± 0.4	15.6 ± 0.3 **	15.9 ± 0.3
MCV (fL)	49.9 ± 0.5	50.2 ± 0.5	50.6 ± 0.7 *	50.4 ± 0.6	50.3 ± 0.3	50.9 ± 0.4 **
MCH (pg)	17.0 ± 0.2	17.1 ± 0.2	17.2 ± 0.2	17.1 ± 0.2	17.1 ± 0.2	17.4 ± 0.1 **
Prothrombin time (sec)	17.2 ± 2.2	17.6 ± 2.7	17.3 ± 1.9	15.0 ± 0.4 **	15.0 ± 0.5 **	15.5 ± 0.5
APTT (sec)	26.5 ± 2.1	27.5 ± 2.7	26.5 ± 3.3	22.4 ± 2.0 **	21.3 ± 2.1 **	22.2 ± 3.0 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 8 HEMATOLOGY OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	10	10	10	10	10	9
Prothrombin time (sec)	15.0 ± 0.6	14.3 ± 0.7 *	15.5 ± 0.6	14.9 ± 0.8	15.1 ± 0.5	15.3 ± 0.4

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 9 BIOCHEMISTRY OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOAVETATE

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	#	#	9	#	#	9
Total protein (g/dL)	6.4 ± 0.1	6.2 ± 0.2	6.2 ± 0.3	6.2 ± 0.2	6.1 ± 0.1 **	6.0 ± 0.1 **
Albumin (g/dL)	4.0 ± 0.1	3.9 ± 0.1	3.9 ± 0.2	3.9 ± 0.1	3.8 ± 0.1 *	3.7 ± 0.1 **
T-Cholesterol (mg/dL)	68 ± 5	62 ± 4 *	64 ± 6	63 ± 4	64 ± 4	60 ± 5 **
GOT (IU/L)	81 ± 17	77 ± 21	75 ± 24	64 ± 14	60 ± 18	54 ± 12 **
GPT (IU/L)	51 ± 8	51 ± 10	48 ± 9	44 ± 6	41 ± 10 *	40 ± 4 *
Urea Nitrogen (mg/dL)	17.7 ± 1.6	19.4 ± 2.1	20.1 ± 1.1 **	20.5 ± 0.9 **	20.4 ± 1.6 **	21.2 ± 1.8 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 10 BIOCHEMISTRY OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOAVETATE

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	#	#	#	#	#	9
Total protein (g/dL)	6.1 ± 0.3	6.0 ± 0.1	5.9 ± 0.2	5.8 ± 0.3 **	5.7 ± 0.2 **	5.6 ± 0.2 **
Albumin (g/dL)	3.8 ± 0.2	3.7 ± 0.1	3.6 ± 0.1 *	3.6 ± 0.2 **	3.5 ± 0.1 **	3.5 ± 0.1 **
ALP (IU/L)	169 ± 18	164 ± 18	167 ± 13	170 ± 16	173 ± 13	203 ± 15 **
Urea Nitrogen (mg/dL)	20.0 ± 1.8	20.2 ± 1.4	22.1 ± 1.3 *	21.6 ± 1.5	22.1 ± 2.3 *	22.3 ± 1.5 *

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 11 URINALYSIS OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACTATE

Group		Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
Number of examined animals		10	10	10	10	10	10
	Grade						
pH	6.0	0	0	0	0 *	0	0 **
	6.5	0	0	0	0	0	0
	7.0	0	1	0	0	0	2
	7.5	0	0	1	5	4	5
	8.0	5	5	6	3	4	0
	8.5	5	4	3	2	2	3
Protein	−	0	0	0	0 **	0 **	0 **
	±	0	0	0	0	0	0
	+	9	6	6	1	2	3
	2+	1	4	4	9	8	7
	3+	0	0	0	0	0	0
	4+	0	0	0	0	0	0
Ketone body	−	6	1	0 *	0 *	0 *	1
	±	2	7	3	5	4	4
	+	1	2	6	3	3	3
	2+	1	0	1	2	3	1
	3+	0	0	0	0	0	1
	4+	0	0	0	0	0	0

Significant difference : * : $p<0.05$ ** : $p<0.01$ Chi square test

TABLE 12 URINALYSIS OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACTATE

Group		Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
Number of examined animals		10	10	10	10	10	9
	Grade						
Protein	−	0	0	0 *	0 **	0 **	0 **
	±	3	0	0	0	0	0
	+	7	10	6	4	4	2
	2+	0	0	4	6	6	7
	3+	0	0	0	0	0	0
	4+	0	0	0	0	0	0
Ketone body	−	4	3	0 *	0 *	0	0 *
	±	6	7	10	10	9	6
	+	0	0	0	0	1	3
	2+	0	0	0	0	0	0
	3+	0	0	0	0	0	0
	4+	0	0	0	0	0	0

Significant difference : * : $p<0.05$ ** : $p<0.01$ Chi square test

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

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	10	10	10	10	10	10
Body weight (g)	308 ± 11	294 ± 14	285 ± 11 **	284 ± 14 **	274 ± 14 **	256 ± 19 **
Thymus (g)	0.226 ± 0.036	0.220 ± 0.031	0.210 ± 0.022	0.210 ± 0.032	0.189 ± 0.019 *	0.174 ± 0.028 **
Thymus (%)	0.073 ± 0.011	0.075 ± 0.008	0.074 ± 0.006	0.074 ± 0.009	0.069 ± 0.006	0.068 ± 0.007
Adrenals (g)	0.047 ± 0.004	0.050 ± 0.010	0.048 ± 0.004	0.047 ± 0.004	0.046 ± 0.003	0.044 ± 0.003
Adrenals (%)	0.015 ± 0.001	0.017 ± 0.004	0.017 ± 0.001 *	0.016 ± 0.002	0.017 ± 0.001 *	0.017 ± 0.002 **
Testes (g)	3.043 ± 0.175	3.087 ± 0.146	3.029 ± 0.094	3.030 ± 0.088	2.975 ± 0.158	2.919 ± 0.107
Testes (%)	0.990 ± 0.054	1.050 ± 0.032	1.063 ± 0.028 *	1.067 ± 0.030 *	1.087 ± 0.056 **	1.147 ± 0.081 **
Heart (g)	0.949 ± 0.064	0.929 ± 0.060	0.885 ± 0.036 *	0.875 ± 0.046 *	0.864 ± 0.051 **	0.799 ± 0.057 **
Heart (%)	0.308 ± 0.012	0.316 ± 0.016	0.311 ± 0.015	0.308 ± 0.013	0.316 ± 0.012	0.313 ± 0.009
Lungs (g)	1.061 ± 0.053	1.006 ± 0.047	1.000 ± 0.044	0.990 ± 0.048 *	0.979 ± 0.076 **	0.936 ± 0.063 **
Lungs (%)	0.345 ± 0.011	0.342 ± 0.011	0.351 ± 0.014	0.348 ± 0.009	0.357 ± 0.016	0.367 ± 0.012 **
Kidneys (g)	1.834 ± 0.064	1.817 ± 0.111	1.803 ± 0.084	1.837 ± 0.116	1.820 ± 0.127	1.709 ± 0.142
Kidneys (%)	0.596 ± 0.013	0.618 ± 0.021	0.633 ± 0.024 **	0.646 ± 0.028 **	0.664 ± 0.024 **	0.669 ± 0.026 **
Spleen (g)	0.572 ± 0.029	0.540 ± 0.041	0.530 ± 0.034	0.523 ± 0.032 *	0.522 ± 0.031 *	0.498 ± 0.052 **
Spleen (%)	0.186 ± 0.005	0.183 ± 0.006	0.186 ± 0.009	0.184 ± 0.004	0.191 ± 0.006	0.195 ± 0.009 *
Liver (g)	7.632 ± 0.219	7.276 ± 0.430	7.141 ± 0.383	6.918 ± 0.375 **	6.794 ± 0.497 **	6.158 ± 0.688 **
Liver (%)	2.482 ± 0.069	2.474 ± 0.090	2.506 ± 0.103	2.433 ± 0.032	2.479 ± 0.088	2.405 ± 0.139
Brain (g)	1.920 ± 0.037	1.920 ± 0.044	1.901 ± 0.043	1.908 ± 0.038	1.899 ± 0.037	1.858 ± 0.058 *
Brain (%)	0.624 ± 0.019	0.654 ± 0.034	0.668 ± 0.020 *	0.673 ± 0.034 **	0.695 ± 0.026 **	0.730 ± 0.045 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 14 ORGAN WEIGHTS OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Group Name	Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
No. of examined animals	10	10	10	10	10	9
Body weight (g)	157 ± 12	160 ± 10	161 ± 10	160 ± 7	153 ± 11	153 ± 12
Adrenals (g)	0.055 ± 0.005	0.052 ± 0.005	0.052 ± 0.004	0.049 ± 0.004 **	0.050 ± 0.004 *	0.047 ± 0.006 **
Adrenals (%)	0.035 ± 0.003	0.032 ± 0.004	0.032 ± 0.002	0.030 ± 0.003 **	0.033 ± 0.004	0.031 ± 0.005 *
Heart (g)	0.596 ± 0.041	0.593 ± 0.033	0.576 ± 0.031	0.582 ± 0.032	0.574 ± 0.040	0.561 ± 0.042
Heart (%)	0.380 ± 0.021	0.370 ± 0.013	0.358 ± 0.015 **	0.363 ± 0.013	0.375 ± 0.014	0.368 ± 0.018
Kidneys (g)	1.087 ± 0.069	1.160 ± 0.048	1.147 ± 0.076	1.199 ± 0.056 **	1.168 ± 0.035 *	1.175 ± 0.083 *
Kidneys (%)	0.695 ± 0.036	0.725 ± 0.037	0.712 ± 0.031	0.748 ± 0.023 *	0.764 ± 0.055 **	0.771 ± 0.043 **
Liver (g)	3.883 ± 0.343	3.844 ± 0.285	3.737 ± 0.194	3.778 ± 0.221	3.652 ± 0.269	3.553 ± 0.270
Liver (%)	2.475 ± 0.094	2.398 ± 0.097	2.319 ± 0.076 **	2.356 ± 0.112 *	2.380 ± 0.058	2.328 ± 0.046 **

Mean ± S.D.

*) Significant difference, $p<0.05$ (Test of Dunnett)

**) Significant difference, $p<0.01$ (Test of Dunnett)

TABLE 15 INCIDENCES OF SELECTED LESIONS OF MALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Group		Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
Number of examined animals		10	10	10	10	10	10
Organ Findings	Grade of Nonneoplastic finding						
Kidney							
Papillary necrosis	1+	0	0	1	0	0	2
Grade	1+: Slight	2+: Moderate	3+: Marked	4+: Severe			
Significant difference	* : p<0.05	** : p<0.01	Chi square test for non-neoplastic lesion				

TABLE 16 INCIDENCES OF SELECTED LESIONS OF FEMALE RATS IN THE 13-WEEK DRINKING WATER STUDY OF METHYL ACETOACETATE

Group		Control	2500 ppm	5000 ppm	10000 ppm	20000 ppm	40000 ppm
Number of examined animals		10	10	10	10	10	10
Organ Findings	Grade of Nonneoplastic finding						
Kidney							
Papillary necrosis	1+	0	0	0	0	2	5 *
Grade	1+: Slight	2+: Moderate	3+: Marked	4+: Severe			
Significant difference	* : p<0.05	** : p<0.01	Chi square test for non-neoplastic lesion				