

# Supplementary Materials: Dose-Response Study of Microcystin Congeners MCLA, MCLR, MCLY, MCRR, and MCYR Administered Orally to Mice

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Table S1. Summary of data for MCLA<sup>1</sup>.

Male					
Dose	Control	0.5 mg/kg	1 mg/kg	3 mg/kg	7 mg/kg
Number of animals	24	12	12	6	8
Morbidity (%)	0	0	0	0	100.0 ***
Weight Change (g.)	-1.89 ± 0.15	-2.26 ± 0.20	-1.64 ± 0.20	-2.63 ± 0.26 **	-1.42 ± 0.24
Liver weight (g.)	1.07 ± 0.02	1.13 ± 0.03	1.12 ± 0.03	1.17 ± 0.05	1.88 ± 0.04 ***
Liver/body weight	4.97 ± 0.10	5.02 ± 0.14	5.09 ± 0.14	5.78 ± 0.18 ***	8.96 ± 0.17 ***
ALT (log <sub>10</sub> (IU/L))	1.76 ± 0.06	1.65 ± 0.08	1.67 ± 0.08	3.47 ± 0.12 ***	4.05 ± 0.17 ***
AST (log <sub>10</sub> (IU/L))	2.06 ± 0.06	1.98 ± 0.08	2.01 ± 0.08	3.51 ± 0.12 ***	3.84 ± 0.16 ***
GLDH (log <sub>10</sub> (IU/L))	1.28 ± 0.03	1.22 ± 0.05	1.17 ± 0.05	2.37 ± 0.08 ***	2.44 ± 0.09 ***
Liver score	2.92 ± 0.41	4.18 ± 0.62	3.00 ± 0.43	9.67 ± 0.33 **	16.00 ± 0.00 ***
BUN (mg/dL)	8.69 ± 0.66	10.19 ± 0.81 *	9.07 ± 0.81	8.26 ± 0.97	13.24 ± 1.27 ***
Cr (mg/dL)	0.50 ± 0.02	0.49 ± 0.03	0.50 ± 0.03	0.42 ± 0.03 **	0.53 ± 0.04
BUN_Cr	17.63 ± 1.03	20.22 ± 1.36 *	17.56 ± 1.36	19.08 ± 1.72	24.65 ± 2.31 **
Albumin (g/dL)	3.65 ± 0.09	3.70 ± 0.11	3.63 ± 0.11	3.63 ± 0.14	2.83 ± 0.19 ***
Globulin(g/dL)	2.39 ± 0.39	2.44 ± 0.40	2.23 ± 0.40	2.16 ± 0.41	1.62 ± 0.43 ***
Total protein (g/L)	6.04 ± 0.40	6.17 ± 0.43	5.89 ± 0.43	5.81 ± 0.45	4.43 ± 0.52 ***
Glucose (mg/dL)	238.33 ± 6.56	185.60 ± 9.28 ***	228.04 ± 9.28	110.01 ± 13.13 ***	124.09 ± 18.57 ***
Total bilirubin (mg/dL)	0.12 ± 0.12	0.11 ± 0.16	0.07 ± 0.16	2.02 ± 0.24 ***	1.12 ± 0.31 **

  

Female					
Dose	Control	0.5 mg/kg	1 mg/kg	3 mg/kg	7 mg/kg
Number of animals	24	12	12	6	8
Morbidity (%)	0	0	0	0	62.5 **
Weight Change (g.)	-1.41 ± 0.08	-1.37 ± 0.11	-1.43 ± 0.11	-2.47 ± 0.16 ***	-2.06 ± 0.14 ***
Liver weight (g.)	0.80 ± 0.03	0.83 ± 0.04	0.88 ± 0.04 *	0.97 ± 0.05 ***	1.21 ± 0.04 ***
Liver/body weight	4.60 ± 0.11	4.64 ± 0.15	4.83 ± 0.15	6.04 ± 0.19 ***	7.25 ± 0.16 ***
ALT (log <sub>10</sub> (IU/L))	1.89 ± 0.13	2.05 ± 0.18	1.85 ± 0.18	3.37 ± 0.24 ***	3.90 ± 0.21 ***
AST (log <sub>10</sub> (IU/L))	2.26 ± 0.08	2.42 ± 0.12	2.21 ± 0.12	3.58 ± 0.16 ***	4.38 ± 0.17 ***
GLDH (log <sub>10</sub> (IU/L))	1.39 ± 0.09	1.48 ± 0.13	1.33 ± 0.13	1.82 ± 0.17 *	1.79 ± 0.18 *
Liver score	1.00 ± 0.36	2.50 ± 0.54	3.67 ± 0.59	9.50 ± 0.22 **	13.75 ± 1.40 ***
BUN (mg/dL)	8.91 ± 0.54	8.78 ± 0.77	8.77 ± 0.77	8.89 ± 1.07	11.88 ± 0.95 **
Cr (mg/dL)	0.51 ± 0.02	0.50 ± 0.03	0.50 ± 0.03	0.41 ± 0.04 **	0.39 ± 0.03 ***
BUN_Cr	17.54 ± 0.77	18.17 ± 1.09	17.99 ± 1.09	21.63 ± 1.55 *	29.24 ± 1.43 ***
Albumin (g/dL)	3.76 ± 0.25	3.66 ± 0.32	3.78 ± 0.32	3.43 ± 0.39	4.46 ± 0.34 *
Globulin(g/dL)	2.20 ± 0.42	2.28 ± 0.43	2.28 ± 0.43	2.14 ± 0.44	1.97 ± 0.44
Total protein (g/L)	5.91 ± 0.41	5.98 ± 0.48	6.09 ± 0.48	5.67 ± 0.56	6.42 ± 0.50
Glucose (mg/dL)	208.76 ± 12.86	199.74 ± 16.15	213.46 ± 16.15	102.60 ± 19.65 ***	88.50 ± 17.45 ***
Total bilirubin (mg/dL)	0.12 ± 0.15	0.10 ± 0.19	0.15 ± 0.20	2.72 ± 0.30 ***	4.33 ± 0.25 ***

All significance tests of difference from control. Mortality statistical significance by Fisher's exact test; liver score by Cochran-Mantel-Haenszel chi-square; \*  $p \leq 0.05$  for differences from controls; \*\*  $p \leq 0.01$  for differences from controls; \*\*\*  $p \leq 0.001$  for differences from controls.

Table S2. Summary of data for MCLR<sup>1</sup>.

## MCLR

Male								
Dose	Control	0.5 mg/kg	1 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg	9 mg/kg	11 mg/kg
Number of animals	24	6	6	12	6	14	6	6
Moribundity (%)	0	0	0	0	33.3	28.6 *	100.0 **	100.0 **
Weight Change (g.)	-1.96 ± 0.24	-2.01 ± 0.38	-1.90 ± 0.38	-2.01 ± 0.29	-2.96 ± 0.35 **	-2.74 ± 0.27 **	-1.67 ± 0.37	-1.08 ± 0.35 **
Liver weight (g.)	1.03 ± 0.04	1.09 ± 0.09	1.23 ± 0.09 *	1.07 ± 0.06	1.29 ± 0.08 **	1.25 ± 0.06 **	1.69 ± 0.09 ***	1.82 ± 0.08 ***
Liver/body weight	5.02 ± 0.25	5.16 ± 0.45	5.31 ± 0.43	5.24 ± 0.31	6.58 ± 0.39 ***	6.54 ± 0.29 ***	8.33 ± 0.42 ***	8.81 ± 0.39 ***
ALT (log <sub>10</sub> (IU/L))	1.76 ± 0.16	1.82 ± 0.28	1.80 ± 0.28	2.09 ± 0.21	2.98 ± 0.26 ***	3.31 ± 0.19 ***	3.68 ± 0.30 ***	3.31 ± 0.28 ***
AST (log <sub>10</sub> (IU/L))	2.08 ± 0.12	2.14 ± 0.22	2.01 ± 0.22	2.24 ± 0.16	2.76 ± 0.20 **	2.91 ± 0.14 ***	3.22 ± 0.24 ***	2.91 ± 0.22 ***
GLDH (log <sub>10</sub> (IU/L))	1.34 ± 0.11	1.41 ± 0.19	1.32 ± 0.19	1.52 ± 0.14	1.86 ± 0.18 **	2.14 ± 0.13 ***	2.22 ± 0.20 *	1.70 ± 0.19
Liver score	3.79 ± 0.68	5.50 ± 0.92	5.33 ± 0.76	4.42 ± 1.16	11.00 ± 2.53 **	12.07 ± 0.97 ***	15.83 ± 0.17 **	16.00 ± 0.00 **
BUN (mg/dL)	9.28 ± 0.33	9.87 ± 0.66	9.97 ± 0.66	10.06 ± 0.46	9.53 ± 0.66	10.58 ± 0.45 *	9.25 ± 0.80	10.53 ± 0.72
Cr (mg/dL)	0.46 ± 0.03	0.50 ± 0.04	0.50 ± 0.04	0.48 ± 0.03	0.44 ± 0.04	0.45 ± 0.03	0.39 ± 0.04	0.52 ± 0.04
BUN_Cr	20.63 ± 1.72	19.52 ± 3.23	19.81 ± 3.23	21.44 ± 2.30	24.20 ± 3.02	24.00 ± 2.11	35.86 ± 3.58 ***	21.04 ± 3.25
Albumin (g/dL)	3.45 ± 0.16	3.68 ± 0.23	3.71 ± 0.23	3.64 ± 0.19	3.44 ± 0.22	3.41 ± 0.17	2.51 ± 0.25 ***	3.05 ± 0.23
Globulin (g/dL)	1.93 ± 0.18	2.17 ± 0.22	2.22 ± 0.22	2.12 ± 0.19	1.88 ± 0.21	1.88 ± 0.18	1.43 ± 0.23 **	1.78 ± 0.22
Total protein (g/L)	5.42 ± 0.24	5.85 ± 0.36	5.93 ± 0.36	5.72 ± 0.28	5.24 ± 0.34	5.30 ± 0.26	3.88 ± 0.39 ***	4.74 ± 0.36 *
Glucose (mg/dL)	192.76 ± 15.57	231.82 ± 26.02	188.78 ± 26.02	211.98 ± 19.52	153.58 ± 24.25	102.58 ± 18.92 ***	157.90 ± 28.03	168.82 ± 25.79
Total bilirubin (mg/dL)	0.16 ± 0.04	0.12 ± 0.06	0.18 ± 0.06	0.15 ± 0.05	0.35 ± 0.07 **	0.29 ± 0.04 **	0.21 ± 0.07	0.33 ± 0.06 **

  

Female								
Dose	Control	0.5 mg/kg	1 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg	9 mg/kg	11 mg/kg
Number of animals	24	6	6	12	6	15	9	6
Moribundity (%)	0	0	0	0	0	6.7	100.0 **	100.0 **
Weight Change (g.)	-1.60 ± 0.11	-1.69 ± 0.20	-1.31 ± 0.20	-1.50 ± 0.14	-2.59 ± 0.19	-2.69 ± 0.13 ***	-0.45 ± 0.17 ***	-0.89 ± 0.21 **
Liver weight (g.)	0.81 ± 0.03	0.89 ± 0.05	0.87 ± 0.05	0.82 ± 0.04	0.81 ± 0.05	0.92 ± 0.03 **	1.44 ± 0.04 ***	1.39 ± 0.05 ***
Liver/body weight	4.60 ± 0.18	4.87 ± 0.29	4.65 ± 0.29	4.75 ± 0.22	4.98 ± 0.27	5.62 ± 0.20 ***	8.04 ± 0.24 ***	7.61 ± 0.27 ***
ALT (log <sub>10</sub> (IU/L))	1.87 ± 0.13	1.69 ± 0.31	1.85 ± 0.26	1.90 ± 0.18	2.94 ± 0.25 ***	3.41 ± 0.16 ***	3.35 ± 0.25 ***	3.38 ± 0.29 ***
AST (log <sub>10</sub> (IU/L))	2.24 ± 0.11	1.95 ± 0.26	2.14 ± 0.22	2.20 ± 0.15	2.80 ± 0.21 *	3.17 ± 0.13 ***	3.22 ± 0.21 ***	3.23 ± 0.26 ***
GLDH (log <sub>10</sub> (IU/L))	1.40 ± 0.10	1.08 ± 0.22	1.31 ± 0.19	1.37 ± 0.13	2.05 ± 0.18 **	2.31 ± 0.12 ***	1.78 ± 0.18	1.61 ± 0.21
Liver score	0.79 ± 0.32	3.83 ± 0.17	3.83 ± 0.17	1.83 ± 0.51	9.00 ± 1.21 **	9.20 ± 0.82 ***	16.00 ± 0.00 ***	16.00 ± 0.00 **
BUN (mg/dL)	8.55 ± 0.61	8.04 ± 1.36	9.41 ± 1.17	9.08 ± 0.83	9.41 ± 1.10	10.66 ± 0.72 *	9.88 ± 1.11	11.41 ± 1.30 *

Cr (mg/dL)	0.49 ± 0.03	0.43 ± 0.05	0.49 ± 0.04	0.48 ± 0.03	0.49 ± 0.04	0.49 ± 0.03	0.51 ± 0.04	0.52 ± 0.04
BUN_Cr	17.25 ± 0.99	18.76 ± 2.24	18.80 ± 1.92	18.11 ± 1.34	20.41 ± 1.80	22.24 ± 1.18 ***	21.89 ± 1.81 *	24.06 ± 2.14 **
Albumin (g/dL)	3.73 ± 0.16	3.29 ± 0.29	3.51 ± 0.26	3.86 ± 0.20	3.89 ± 0.24	3.69 ± 0.18	2.93 ± 0.25 **	3.12 ± 0.28 *
Globulin(g/dL)	1.83 ± 0.22	1.50 ± 0.27	1.66 ± 0.26	1.89 ± 0.23	1.92 ± 0.25	1.67 ± 0.22	1.43 ± 0.25 *	1.45 ± 0.26 *
Total protein (g/L)	5.52 ± 0.27	4.78 ± 0.47	5.15 ± 0.42	5.73 ± 0.33	5.79 ± 0.39	5.36 ± 0.30	4.34 ± 0.39 **	4.55 ± 0.44 *
Glucose (mg/dL)	211.88 ± 16.16	176.12 ± 38.41	222.87 ± 32.37	164.91 ± 22.19	104.46 ± 30.98 **	100.47 ± 19.79 ***	217.97 ± 31.12	135.09 ± 37.25
Total bilirubin (mg/dL)	0.17 ± 0.05	0.19 ± 0.09	0.17 ± 0.08	0.18 ± 0.06	0.17 ± 0.07	0.20 ± 0.05	0.32 ± 0.07 *	0.20 ± 0.08

All significance tests of difference from control. Mortality statistical significance by Fisher's exact test; liver score by Cochran-Mantel-Haenszel chi-square; \*  $p \leq 0.05$  for differences from controls; \*\*  $p \leq 0.01$  for differences from controls; \*\*\*  $p \leq 0.001$  for differences from controls.

Table S3. Summary of data for MCLY<sup>1</sup>.

<b>Male</b>					
Dose	Control	1 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg
Number of animals	27	6	14	13	8
Morbidity (%)	0	0	0	0	25
Weight Change (g.)	-2.01 ± 0.16	-1.31 ± 0.31 *	-1.74 ± 0.21	-2.72 ± 0.21 **	-2.18 ± 0.26
Liver weight (g.)	1.09 ± 0.08	0.89 ± 0.12	1.09 ± 0.09	1.15 ± 0.09	1.45 ± 0.10 ***
Liver/body weight	5.01 ± 0.28	4.66 ± 0.43	4.94 ± 0.33	5.39 ± 0.24	6.67 ± 0.37 ***
ALT (log <sub>10</sub> (IU/L))	1.64 ± 0.07	1.83 ± 0.15	1.63 ± 0.10	2.08 ± 0.10 ***	2.38 ± 0.15 ***
AST (log <sub>10</sub> (IU/L))	2.02 ± 0.05	2.04 ± 0.11	1.90 ± 0.07	2.25 ± 0.07 *	2.44 ± 0.11 **
GLDH (log <sub>10</sub> (IU/L))	1.22 ± 0.06	1.32 ± 0.13	1.21 ± 0.09	1.65 ± 0.09 ***	1.95 ± 0.13 ***
Liver score	3.48 ± 0.51	3.00 ± 1.00	1.93 ± 0.54 *	5.62 ± 0.98	7.75 ± 2.28 *
BUN (mg/dL)	8.92 ± 0.40	9.27 ± 0.85	9.93 ± 0.56	9.31 ± 0.58	10.51 ± 0.82
Cr (mg/dL)	0.52 ± 0.05	0.49 ± 0.06	0.51 ± 0.05	0.51 ± 0.05	0.50 ± 0.06
BUN_Cr	17.64 ± 1.37	21.31 ± 2.00	19.70 ± 1.61	19.89 ± 1.60	20.30 ± 1.88
Albumin (g/dL)	3.57 ± 0.08	3.58 ± 0.15	3.62 ± 0.11	3.62 ± 0.11	3.57 ± 0.14
Globulin(g/dL)	2.05 ± 0.17	1.95 ± 0.19	2.11 ± 0.18	2.11 ± 0.18	1.95 ± 0.19
Total protein (g/L)	5.58 ± 0.13	5.54 ± 0.25	5.70 ± 0.17	5.72 ± 0.18	5.53 ± 0.23
Glucose (mg/dL)	205.32 ± 7.60	212.96 ± 16.09	202.53 ± 10.51	151.87 ± 10.86 ***	130.77 ± 15.49 ***
Total bilirubin (mg/dL)	0.23 ± 0.07	0.01 ± 0.10 **	0.21 ± 0.08	0.26 ± 0.08	0.22 ± 0.09
<b>Female</b>					
Dose	Control	1 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg
Number of animals	27	6	14	14	8
Morbidity (%)	0	0	0	0	0
Weight Change (g.)	-1.41 ± 0.10	-1.20 ± 0.21	-1.57 ± 0.14	-1.90 ± 0.14	-2.53 ± 0.18 ***
Liver weight (g.)	0.83 ± 0.04	0.78 ± 0.05	0.88 ± 0.04	0.95 ± 0.04 ***	0.94 ± 0.05 **
Liver/body weight	4.64 ± 0.16	4.35 ± 0.26	4.86 ± 0.19	5.18 ± 0.19 **	5.72 ± 0.22 ***
ALT (log <sub>10</sub> (IU/L))	1.87 ± 0.13	1.46 ± 0.26	1.98 ± 0.18	2.07 ± 0.18	2.41 ± 0.22 *
AST (log <sub>10</sub> (IU/L))	2.26 ± 0.09	1.98 ± 0.18	2.31 ± 0.12	2.38 ± 0.12	2.75 ± 0.16 **
GLDH (log <sub>10</sub> (IU/L))	1.33 ± 0.10	1.00 ± 0.19	1.42 ± 0.13	1.65 ± 0.13 *	1.70 ± 0.16 *
Liver score	0.85 ± 0.30	1.67 ± 1.09	2.36 ± 0.62	5.14 ± 0.74 **	5.50 ± 1.59 **
BUN (mg/dL)	9.21 ± 0.49	9.46 ± 0.91	7.71 ± 0.64 *	8.61 ± 0.64	8.68 ± 0.76
Cr (mg/dL)	0.55 ± 0.06	0.56 ± 0.07	0.54 ± 0.06	0.55 ± 0.06	0.48 ± 0.07
BUN_Cr	17.09 ± 1.30	17.93 ± 2.02	14.71 ± 1.57	32.76 ± 18.71	33.08 ± 20.56
Albumin (g/dL)	3.78 ± 0.12	3.76 ± 0.20	3.82 ± 0.15	3.72 ± 0.15	3.46 ± 0.17 *
Globulin(g/dL)	1.86 ± 0.22	1.89 ± 0.25	1.85 ± 0.23	1.89 ± 0.23	1.58 ± 0.24 *
Total protein (g/L)	5.59 ± 0.23	5.64 ± 0.34	5.66 ± 0.27	5.59 ± 0.27	5.07 ± 0.30 *
Glucose (mg/dL)	198.85 ± 13.27	234.2 ± 23.53	220.22 ± 16.90	177.18 ± 16.90	133.22 ± 19.74 **
Total bilirubin (mg/dL)	0.18 ± 0.16	0.02 ± 0.28	0.26 ± 0.21	0.59 ± 0.20 *	0.59 ± 0.23

All significance tests of difference from control. Mortality statistical significance by Fisher's exact test; liver score by Cochran-Mantel-Haenszel chi-square; \*  $p \leq 0.05$  for differences from controls; \*\*  $p \leq 0.01$  for differences from controls; \*\*\*  $p \leq 0.001$  for differences from controls.

Table S4. Summary of data for MCRR<sup>1</sup>.

<b>Male</b>					
Dose	Control	7 mg/kg	9 mg/kg	11 mg/kg	22 mg/kg
Number of animals	21	9	6	9	3
Morbidity (%)	0	0	0	0	0
Weight Change (g.)	-1.97 ± 0.17	-1.92 ± 0.22	-1.50 ± 0.29	-2.26 ± 0.24	-2.79 ± 0.35 *
Liver weight (g.)	1.02 ± 0.01	1.03 ± 0.02	1.11 ± 0.03 **	1.09 ± 0.02 *	0.92 ± 0.04 *
Liver/body weight	4.88 ± 0.10	5.01 ± 0.12	5.22 ± 0.15 *	5.02 ± 0.13	4.77 ± 0.18
ALT (log <sub>10</sub> (IU/L))	1.65 ± 0.06	1.89 ± 0.08 *	1.54 ± 0.10	1.55 ± 0.08	1.65 ± 0.15
AST (log <sub>10</sub> (IU/L))	2.04 ± 0.04	2.17 ± 0.07	1.88 ± 0.08	1.96 ± 0.07	2.08 ± 0.11
GLDH (log <sub>10</sub> (IU/L))	1.22 ± 0.04	1.34 ± 0.05 *	1.13 ± 0.07	1.23 ± 0.05	1.30 ± 0.09
Liver score	3.00 ± 0.40	3.00 ± 0.58	3.83 ± 0.31	3.89 ± 0.48	4.00 ± 0.00
BUN (mg/dL)	9.46 ± 0.28	9.45 ± 0.43	7.21 ± 0.53 ***	8.24 ± 0.43 *	9.12 ± 0.74
Cr (mg/dL)	0.55 ± 0.05	0.55 ± 0.05	0.47 ± 0.06 *	0.48 ± 0.05 *	0.53 ± 0.06
BUN_Cr	17.7 ± 1.29	17.29 ± 1.44	15.50 ± 1.68	17.39 ± 1.52	17.54 ± 1.85
Albumin (g/dL)	3.61 ± 0.08	3.54 ± 0.11	3.44 ± 0.14	3.58 ± 0.12	3.90 ± 0.18
Globulin(g/dL)	2.03 ± 0.21	1.92 ± 0.21	2.00 ± 0.23	2.22 ± 0.22	2.17 ± 0.24
Total protein (g/L)	5.62 ± 0.19	5.44 ± 0.24	5.49 ± 0.30	5.83 ± 0.25	6.10 ± 0.34
Glucose (mg/dL)	216.88 ± 8.75	224.05 ± 12.60	218.70 ± 16.36	215.71 ± 13.24	183.48 ± 21.35
Total bilirubin (mg/dL)	0.18 ± 0.06	0.15 ± 0.08	0.28 ± 0.09	0.26 ± 0.08	0.25 ± 0.12

  

<b>Female</b>					
Dose	Control	7 mg/kg	9 mg/kg	11 mg/kg	22 mg/kg
Number of animals	21	8	6	9	3
Morbidity (%)	0	0	0	0	0
Weight Change (g.)	-1.30 ± 0.09	-1.51 ± 0.13	-1.89 ± 0.17 **	-1.67 ± 0.14 *	-2.16 ± 0.21 ***
Liver weight (g.)	0.85 ± 0.04	0.85 ± 0.04	0.75 ± 0.05 **	0.82 ± 0.04	0.89 ± 0.05
Liver/body weight	4.73 ± 0.18	4.84 ± 0.19	4.21 ± 0.21 ***	4.51 ± 0.20 *	4.95 ± 0.22
ALT (log <sub>10</sub> (IU/L))	1.81 ± 0.07	1.79 ± 0.12	1.60 ± 0.14	1.76 ± 0.11	1.76 ± 0.19
AST (log <sub>10</sub> (IU/L))	2.24 ± 0.06	2.16 ± 0.10	2.17 ± 0.12	2.08 ± 0.10	1.98 ± 0.17
GLDH (log <sub>10</sub> (IU/L))	1.29 ± 0.05	1.34 ± 0.09	1.19 ± 0.10	1.26 ± 0.08	1.27 ± 0.14
Liver score	0.95 ± 0.38	1.25 ± 0.84 **	3.33 ± 1.05	2.11 ± 0.68	5.33 ± 1.33
BUN (mg/dL)	9.34 ± 0.65	8.61 ± 0.85	6.90 ± 1.10 *	7.42 ± 0.88 *	6.10 ± 1.24 **
Cr (mg/dL)	0.58 ± 0.07	0.53 ± 0.07	0.57 ± 0.08	0.61 ± 0.07	0.62 ± 0.08
BUN_Cr	16.19 ± 1.20	16.89 ± 1.46	22.90 ± 23.74	21.73 ± 21.53	15.62 ± 25.83
Albumin (g/dL)	3.87 ± 0.09	3.66 ± 0.14	3.57 ± 0.17	3.70 ± 0.14	3.94 ± 0.23
Globulin(g/dL)	1.88 ± 0.27	1.61 ± 0.28 *	1.81 ± 0.30	1.89 ± 0.28	2.05 ± 0.31
Total protein (g/L)	5.69 ± 0.25	5.25 ± 0.30	5.49 ± 0.36	5.67 ± 0.32	6.02 ± 0.41
Glucose (mg/dL)	214.08 ± 11.46	205.47 ± 15.85	203.03 ± 19.86	224.90 ± 16.37	164.52 ± 24.19 *
Total bilirubin (mg/dL)	0.16 ± 0.04	0.17 ± 0.07	0.29 ± 0.10	0.42 ± 0.06 **	0.30 ± 0.10

All significance tests of difference from control. Mortality statistical significance by Fisher's exact test; liver score by Cochran-Mantel-Haenszel chi-square; \*  $p \leq 0.05$  for differences from controls; \*\*  $p \leq 0.01$  for differences from controls; \*\*\*  $p \leq 0.001$  for differences from controls.

Table S5. Summary of data for MCYR<sup>1</sup>.

<b>Male</b>					
Dose	Control	3 mg/kg	5 mg/kg	7 mg/kg	11 mg/kg
Number of animals	18	6	6	9	6
Morbidity (%)	0	0	0	11.1	33.3
Weight Change (g.)	-1.70 ± 0.20	-1.83 ± 0.34	-1.72 ± 0.34	-2.96 ± 0.28 ***	-2.67 ± 0.34 *
Liver weight (g.)	1.11 ± 0.05	1.06 ± 0.09	1.11 ± 0.09	1.15 ± 0.07	1.49 ± 0.09 ***
Liver/body weight	5.05 ± 0.20	4.84 ± 0.33	5.07 ± 0.33	5.40 ± 0.26	6.66 ± 0.35 ***
ALT (log <sub>10</sub> (IU/L))	2.02 ± 0.18	1.90 ± 0.25	2.07 ± 0.25	2.33 ± 0.21	3.36 ± 0.27 ***
AST (log <sub>10</sub> (IU/L))	2.21 ± 0.10	2.05 ± 0.15	2.27 ± 0.15	2.27 ± 0.12	2.94 ± 0.17 ***
GLDH (log <sub>10</sub> (IU/L))	1.39 ± 0.09	1.24 ± 0.15	1.50 ± 0.15	1.74 ± 0.12 **	2.35 ± 0.16 ***
Liver score	2.17 ± 0.49	2.00 ± 0.93	1.67 ± 1.05	7.89 ± 1.32 **	13.67 ± 0.92 **
BUN (mg/dL)	8.32 ± 1.23	6.25 ± 1.48 *	6.42 ± 1.48	11.47 ± 1.32 ***	11.49 ± 1.55 **
Cr (mg/dL)	0.49 ± 0.02	0.47 ± 0.03	0.49 ± 0.03	0.54 ± 0.03	0.52 ± 0.03
BUN_Cr	16.99 ± 2.02	14.10 ± 2.31 *	13.71 ± 2.31 *	20.95 ± 2.32 ***	21.96 ± 2.40 **
Albumin (g/dL)	3.61 ± 0.11	3.67 ± 0.16	3.69 ± 0.16	4.08 ± 0.13 ***	4.02 ± 0.18 *
Globulin(g/dL)	1.82 ± 0.20	1.86 ± 0.22	1.88 ± 0.22	2.02 ± 0.21 *	2.08 ± 0.22 *
Total protein (g/L)	5.41 ± 0.14	5.62 ± 0.22	5.66 ± 0.22	6.06 ± 0.18 **	6.18 ± 0.25 **
Glucose (mg/dL)	236.14 ± 7.45	196.00 ± 12.90 *	196.33 ± 12.90 *	145.21 ± 11.17 ***	85.47 ± 15.80 ***
Total bilirubin (mg/dL)	0.27 ± 0.16	0.27 ± 0.17	0.28 ± 0.17	0.38 ± 0.16*	0.41 ± 0.16 *

  

<b>Female</b>					
Dose	Control	3 mg/kg	5 mg/kg	7 mg/kg	11 mg/kg
Number of animals	18	6	6	9	6
Morbidity (%)	0	0	0	0	16.7
Weight Change (g.)	-1.19 ± 0.14	-1.30 ± 0.25	-1.55 ± 0.30	-1.70 ± 0.20 *	-2.08 ± 0.25 **
Liver weight (g.)	0.88 ± 0.02	0.87 ± 0.04	0.98 ± 0.05	0.89 ± 0.03	1.02 ± 0.04 **
Liver/body weight	5.01 ± 0.09	4.75 ± 0.15	5.18 ± 0.19	5.35 ± 0.12 *	6.40 ± 0.15 ***
ALT (log <sub>10</sub> (IU/L))	2.07 ± 0.22	1.87 ± 0.34	2.64 ± 0.38	2.33 ± 0.26	3.50 ± 0.32 ***
AST (log <sub>10</sub> (IU/L))	2.35 ± 0.15	2.09 ± 0.25	2.61 ± 0.29	2.59 ± 0.19	3.41 ± 0.24 ***
GLDH (log <sub>10</sub> (IU/L))	1.42 ± 0.12	1.36 ± 0.20	1.77 ± 0.23	1.59 ± 0.15	2.30 ± 0.19 ***
Liver score	0.00 ± 0.00	0.00 ± 0.00	3.75 ± 2.39	3.89 ± 0.99 **	11.83 ± 1.17 **
BUN (mg/dL)	8.06 ± 0.85	9.05 ± 1.43	9.00 ± 1.75	9.39 ± 1.17	15.08 ± 1.32 ***
Cr (mg/dL)	0.53 ± 0.03	0.52 ± 0.04	0.50 ± 0.05	0.51 ± 0.03	0.49 ± 0.04
BUN_Cr	15.02 ± 1.99	15.86 ± 3.35	16.80 ± 4.11	18.51 ± 2.74	33.28 ± 3.11 ***
Albumin (g/dL)	3.96 ± 0.11	3.84 ± 0.19	3.74 ± 0.23	3.84 ± 0.15	3.39 ± 0.18 **
Globulin(g/dL)	1.61 ± 0.25	1.66 ± 0.27	1.58 ± 0.27	1.57 ± 0.25	1.24 ± 0.26 **
Total protein (g/L)	5.53 ± 0.27	5.54 ± 0.39	5.35 ± 0.42	5.40 ± 0.31	4.61 ± 0.37 *
Glucose (mg/dL)	229.09 ± 19.81	199.66 ± 25.72	150.26 ± 27.57 **	173.09 ± 21.50 **	76.13 ± 24.78 ***
Total bilirubin (mg/dL)	0.29 ± 0.12	0.27 ± 0.14	0.30 ± 0.15	0.27 ± 0.13	0.34 ± 0.14

All significance tests of difference from control. Mortality statistical significance by Fisher's exact test; liver score by Cochran-Mantel-Haenszel chi-square; \*  $p \leq 0.05$  for differences from controls; \*\*  $p \leq 0.01$  for differences from controls; \*\*\*  $p \leq 0.001$  for differences from controls.