

Supplementary Table S6. Time course effects of prior DCA exposure on the incidence of non-neoplastic histopathologic findings in the liver.

Duration of DCA exposure | control dH₂O treatment (weeks) **0 | 93** **4 | 89** **10 | 83** **26 | 67** **52 | 41** **93 | 0**

10 weeks

| No. Examined Microscopically | 10 | 0 | 10 | 0 | 0 | 0 |
|-------------------------------------|-----------|----------|------------------|----------|----------|----------|
| Cytomegaly | 0 (0.0) | | 10 (4.0)* | | | |
| Cytoplasmic Vacuolization | 9 (1.1) | | 10 (4.0) | | | |
| Necrosis, Hepatocellular | 2 (0.2) | | 10 (1.9)* | | | |
| Inflammation, Any | 3 (0.3) | | 6 (0.7) | | | |
| Inflammation, Chronic/Active | 1 (0.1) | | 4 (0.5) | | | |
| Inflammation, Chronic | 1 (0.1) | | 0 (0.0) | | | |
| Inflammation, Subacute | 1 (0.1) | | 2 (0.2) | | | |
| Hemorrhage | 0 (0.0) | | 2 (0.2) | | | |
| Pigmentation NOS | 0 (0.0) | | 6 (0.6)* | | | |

15 weeks

| No. Examined Microscopically | 10 | 0 | 10 | 10 | 0 | 0 |
|-------------------------------------|-----------|----------|------------------|------------------|----------|----------|
| Cytomegaly | 0 (0.0) | | 10 (2.9)* | 10 (3.8)* | | |
| Cytoplasmic Vacuolization | 4 (0.5) | | 10 (2.9) | 10 (3.8) | | |
| Necrosis, Hepatocellular | 1 (0.1) | | 3 (0.5) | 10 (2.0)* | | |
| Inflammation, Any | 1 (0.1) | | 1 (0.1) | 8 (1.2)* | | |
| Inflammation, Chronic/Active | 0 (0.0) | | 1 (0.1) | 6 (1.0)* | | |
| Inflammation, Chronic | 1 (0.1) | | 0 (0.0) | 0 (0.0) | | |
| Inflammation, Subacute | 0 (0.0) | | 0 (0.0) | 2 (0.2) | | |
| Pigmentation NOS | 0 (0.0) | | 2 (0.2) | 3 (0.3) | | |
| Mitotic Alteration | 1 (0.1) | | 0 (0.0) | 0 (0.0) | | |

26 weeks

| No. Examined Microscopically | 10 | 0 | 10 | 10 | 0 | 0 |
|-------------------------------------|-----------|----------|------------------|------------------|----------|----------|
| Cytomegaly | 0 (0.0) | | 10 (2.1)* | 10 (4.0)* | | |
| Cytoplasmic Vacuolization | 6 (0.6) | | 10 (2.3) | 10 (4.0) | | |
| Necrosis, Hepatocellular | 0 (0.0) | | 3 (0.4) | 8 (1.3)* | | |
| Inflammation, Any | 0 (0.0) | | 1 (0.1) | 5 (0.9)* | | |
| Inflammation, Chronic | 0 (0.0) | | 0 (0.0) | 5 (0.9)* | | |
| Inflammation, Subacute | 0 (0.0) | | 1 (0.1) | 0 (0.0) | | |

| | | | | |
|------------------|---------|--|---------|-----------------|
| Pigmentation NOS | 0 (0.0) | | 3 (0.3) | 6 (0.8)* |
|------------------|---------|--|---------|-----------------|

31 weeks

| No. Examined Microscopically | 10 | 0 | 10 | 10 | 10 | 0 |
|------------------------------|---------|---|----------|------------------|------------------|---|
| Cytomegaly | 0 (0.0) | | 4 (0.5) | 10 (3.0)* | 10 (3.9)* | |
| Cytoplasmic Vacuolization | 7 (0.8) | | 10 (1.4) | 10 (3.2) | 10 (3.9) | |
| Necrosis, Hepatocellular | 0 (0.0) | | 1 (0.1) | 0 (0.0) | 7 (1.2)* | |
| Inflammation, Any | 0 (0.0) | | 1 (0.1) | 3 (0.4) | 4 (0.6) | |
| Inflammation, Chronic/Active | 0 (0.0) | | 0 (0.0) | 1 (0.2) | 2 (0.3) | |
| Inflammation, Subacute | 0 (0.0) | | 1 (0.1) | 2 (0.2) | 2 (0.3) | |
| Pigmentation NOS | 0 (0.0) | | 1 (0.1) | 9 (1.3)* | 10 (1.3)* | |
| Lymphocytic Infiltrates | 0 (0.0) | | 0 (0.0) | 1 (0.1) | 1 (0.1) | |
| Focus, Any | 0 | | 1 | 0 | 1 | |
| Eosinophilic Focus | 0 | | 0 | 0 | 1 | |
| Basophilic Focus | 0 | | 1 | 0 | 0 | |

52 weeks

| No. Examined Microscopically | 9 | 0 | 10 | 10 | 10 | 0 |
|------------------------------|---------|---|---------|-----------------|------------------|---|
| Cytomegaly | 1 (0.1) | | 0 (0.0) | 8 (1.0)* | 10 (3.6)* | |
| Cytoplasmic Vacuolization | 5 (1.0) | | 6 (0.8) | 10 (1.8) | 10 (3.6) | |
| Necrosis, Hepatocellular | 3 (0.6) | | 0 (0.0) | 1 (0.1) | 7 (0.9) | |
| Inflammation, Any | 1 (0.3) | | 0 (0.0) | 1 (0.1) | 2 (0.2) | |
| Inflammation, Chronic | 0 (0.0) | | 0 (0.0) | 1 (0.1) | 0 (0.0) | |
| Inflammation, Chronic/Active | 1 (0.3) | | 0 (0.0) | 0 (0.0) | 1 (0.1) | |
| Inflammation, Subacute | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 1 (0.1) | |
| Pigmentation NOS | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 6 (1.0)* | |
| Lymphocytic Infiltrates | 0 (0.0) | | 0 (0.0) | 2 (0.4) | 0 (0.0) | |
| Hyperplasia, Hepatocellular | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 2 (0.5) | |
| Focus, Any | 0 | | 0 | 4 | 4 | |
| Eosinophilic Focus | 0 | | 0 | 0 | 3 | |
| Basophilic Focus | 0 | | 0 | 4 | 1 | |

57 weeks

| No. Examined Microscopically | 10 | 0 | 10 | 9 | 9 | 10 |
|-------------------------------------|-----------|----------|-----------|----------|-----------------|------------------|
| Cytomegaly | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 9 (4.0)* | 10 (3.8)* |
| Cytoplasmic Vacuolization | 5 (0.8) | | 3 (0.3) | 9 (1.7) | 9 (3.0) | 10 (3.6) |
| Necrosis, Hepatocellular | 2 (0.6) | | 0 (0.0) | 1 (0.1) | 4 (0.6) | 9 (1.4)* |
| Inflammation, Chronic/Active | 3 (0.7) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pigmentation NOS | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| Lymphocytic Infiltrates | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Perivascular Amyloidosis | 2 (0.6) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Congestion | 0 (0.0) | | 2 (0.6) | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Focus, Any | 0 | | 1 | 2 | 4 | 1 |
| Eosinophilic Focus | 0 | | 0 | 0 | 3 | 1 |
| Basophilic Focus | 0 | | 1 | 2 | 0 | 0 |
| Mixed Cell Focus | 0 | | 0 | 0 | 1 | 0 |

78 weeks

| No. Examined Microscopically | 6 | 0 | 6 | 6 | 6 | 6 |
|-------------------------------------|----------|----------|----------|----------|----------|----------|
| Cytomegaly | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 1 (0.2) | 4 (2.7) |
| Cytoplasmic Vacuolization | 1 (0.3) | | 1 (0.2) | 4 (1.0) | 4 (1.0) | 4 (2.5) |
| Hyperplasia, Bile Duct | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Hyperplasia, Hepatocellular | 0 | | 0 | 1 | 1 | 0 |
| Necrosis, Hepatocellular | 1 (0.3) | | 3 (0.7) | 1 (0.7) | 3 (0.7) | 1 (0.2) |
| Inflammation, Subacute | 1 (0.3) | | 2 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pigmentation NOS | 0 (0.0) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Lymphocytic Infiltrates | 0 (0.0) | | 1 (0.3) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Sinusoidal Dilatation | 0 (0.0) | | 1 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Focus, Any | 1 | | 3 | 3 | 0 | 0 |
| Eosinophilic Focus | 0 | | 1 | 0 | 0 | 0 |
| Basophilic Focus | 1 | | 3 | 3 | 0 | 0 |
| Vacuolated Cell Focus | 0 | | 1 | 1 | 0 | 0 |

93 weeks

| No. Examined Microscopically | 25 | 23 | 25 | 24 | 17 | 17 |
|-------------------------------------|-----------|------------------|-----------|------------------|-----------|------------------|
| Cytomegaly | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.3) | 12 (2.1)* |
| Cytoplasmic Vacuolization | 18 (1.4) | 16 (1.2) | 19 (1.3) | 18 (1.3) | 11 (1.3) | 12 (2.2) |
| Necrosis, Hepatocellular | 3 (0.2) | 13 (1.1)* | 10 (0.8) | 11 (0.9)* | 5 (0.4) | 6 (0.8) |
| Inflammation, Any | 2 (0.2) | 6 (0.6) | 7 (0.5) | 7 (0.4) | 3 (0.3) | 3 (0.3) |
| Inflammation, Chronic/Active | 2 (0.2) | 6 (0.6) | 7 (0.5) | 5 (0.3) | 3 (0.3) | 2 (0.2) |
| Inflammation, Chronic | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) | 0 (0.0) | 0 (0.0) |
| Inflammation, Subacute | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Mineralization NOS | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Lymphocytic Infiltrates | 4 (0.3) | 4 (0.4) | 7 (0.5) | 3 (0.2) | 0 (0.0) | 1 (0.1) |
| Extramedullary Hematopoiesis | 0 (0.0) | 2 (0.2) | 2 (0.1) | 4 (0.3) | 0 (0.0) | 0 (0.0) |
| Hemorrhage | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hyperplasia, Hepatocellular | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Focus, Any | 2 | 5 | 3 | 2 | 5 | 2 |
| Eosinophilic Focus | 1 | 1 | 0 | 0 | 0 | 1 |
| Basophilic Focus | 0 | 3 | 3 | 2 | 5* | 0 |
| Basophilic Focus, Multiple | 0 | 0 | 1 | 0 | 1 | 0 |
| Clear Cell Focus | 1 | 2 | 0 | 0 | 0 | 1 |
| Clear Cell Focus, Multiple | 1 | 0 | 0 | 0 | 0 | 0 |

Values in parentheses indicate average lesion severity based on a 0-4 scale; NOS, not otherwise specified. Asterisk (*) indicates significant difference compared to control by one-sided Fisher's Exact Test ($P < 0.05$).