**STATISTICAL ANALYSIS**

**IMMUNOTOX STUDY**

**OF**

**PERFLUORODECANOIC ACID**

**(28 DAY EXPOSURE)**

**IN FEMALE HARLAN SPRAGUE-DAWLEY RATS**

**PREPARED FOR**

**National Institute of Environmental Health Sciences**

**National Toxicology Program**

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**TABLE OF CONTENTS**

**Subject Table**

Study 1 Serum IGM ELISA 1

Study 1 Organ Weights 2

Study 1 Body Weights 3

Study 2 T Dependent AB Response Day 4  4

Study 2 Body Weights 5

Study 3Delayed Type Hypersensitivity 6

Study 3 Body Weights 7

Study 4 Keyhole Limpet Hemocyanin 8

Study 4 Body Weights 9

Study 5 T Dependent AB Response Day 4  10

Study 5 Body Weights 11

Study 6 Anti CD3 Proliferation 12

Study 6 DNA Synthesis 13

Study 6 Bone Marrow 14

Study 6 Body Weights 15

Study 7 Mononuclear Phagocytic System 16

Study 7 Body Weights 17

Study 8 Absolute Surface Markers 18

Study 8 %Surface Markers 19

Study 8 Natural Killer Activity 20

Study 8 Body Weights 21

Study 9 Bone Marrow 22

Study 9 % Bone Marrow Differentials  23

Study 9 Absolute Bone Marrow Differentials 24

Study 9 DNA Synthesis 25

Study 9 Body Weights 26

Study 10 T Dependent AB Response Day 4  27

Study 10 Body Weights 28

Study 11 Hematology 29

Study 11 Absolute Leukocyte Differentials 30

Study 11 Reticulocytes 31

Study 11 Organ Weights 32

Study 11 Body Weights 33

**Appendices**

Extreme Values  A

Statistical Methods B

References  C

| **TABLE 1 PFDA SERUM IGM ELISA IN FEMALE RATS  STUDY 1** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **SERUM TITER (LOG2)** | 7.60 ± 0.601 [8] | 7.31 ± 0.206 [8] | 7.34 ± 0.291 [8] | 7.94 ± 0.524 [8] | 0.650 |

| **Parametera** | **Vehicle Control** | **25 mg/kg CPS (ip x6)** | **Trendc** |
| --- | --- | --- | --- |
| **SERUM TITER (LOG2)** | 7.60 ± 0.601 [8] | 1.33 ± 0.329 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 2 PFDA ORGAN WEIGHTS IN FEMALE RATS  STUDY 1** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **BODY WGT (G)** | 217.8 ± 2.940 [8] | 211.5 ± 5.351 [8] | 219.7 ± 3.984 [8] | 223.2 ± 3.292 [8] | 0.239 |
| **LIVER (MG)** | 8390 ± 138.9 [8] | 8342 ± 225.5 [8] | 10114 ± 349.1 [8]\*\* | 11633 ± 332.8 [8]\*\* | <.001 |
| **SPLEEN (MG)** | 592.4 ± 11.09 [8] | 567.5 ± 15.60 [8] | 595.4 ± 22.42 [8] | 595.4 ± 20.85 [8] | 0.827 |
| **THYMUS (MG)** | 292.0 ± 8.896 [8] | 391.6 ± 27.24 [8]\*\* | 379.3 ± 26.49 [8]\* | 352.5 ± 16.79 [8] | 0.049 |
| **LIVER /BODY (%)** | 3.85 ± 0.050 [8] | 3.94 ± 0.043 [8] | 4.60 ± 0.128 [8]\*\* | 5.21 ± 0.104 [8]\*\* | <.001 |
| **SPLEEN /BODY (%)** | 0.27 ± 0.004 [8] | 0.27 ± 0.009 [8] | 0.27 ± 0.007 [8] | 0.27 ± 0.008 [8] | 0.563 |
| **THYMUS /BODY (%)** | 0.14 ± 0.005 [8] | 0.19 ± 0.015 [8]\*\* | 0.17 ± 0.012 [8]\* | 0.16 ± 0.008 [8] | 0.124 |

| **Parametera** | **Vehicle Control** | **25 mg/kg CPS (ip x6)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT (G)** | 217.8 ± 2.940 [8] | 213.6 ± 4.899 [8] | 0.600 |
| **LIVER (MG)** | 8390 ± 138.9 [8] | 8338 ± 218.8 [8] | 0.834 |
| **SPLEEN (MG)** | 592.4 ± 11.09 [8] | 305.4 ± 13.99 [8]\*\* | <.001 |
| **THYMUS (MG)** | 292.0 ± 8.896 [8] | 208.3 ± 20.20 [8]\*\* | 0.006 |
| **LIVER /BODY (%)** | 3.85 ± 0.050 [8] | 3.90 ± 0.049 [8] | 0.599 |
| **SPLEEN /BODY (%)** | 0.27 ± 0.004 [8] | 0.14 ± 0.006 [8]\*\* | <.001 |
| **THYMUS /BODY (%)** | 0.14 ± 0.005 [8] | 0.10 ± 0.008 [8]\*\* | 0.003 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 3 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 1** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 172.7 ± 2.910 [8] | 165.8 ± 4.893 [8] | 171.5 ± 3.841 [8] | 173.1 ± 3.588 [8] | 172.5 ± 2.397 [8] | 171.6 ± 3.475 [8] | 0.481 |
| **BODY WGT DAY 8 (G)** | 190.7 ± 2.817 [8] | 182.0 ± 5.112 [8] | 188.8 ± 3.617 [8] | 191.3 ± 3.268 [8] | 189.0 ± 2.439 [8] | 191.2 ± 3.813 [8] | 0.454 |
| **BODY WGT DAY 15 (G)** | 201.4 ± 2.489 [8] | 194.0 ± 5.089 [8] | 202.2 ± 4.048 [8] | 205.3 ± 2.551 [8] | 202.3 ± 2.886 [8] | 199.1 ± 3.957 [8] | 0.821 |
| **BODY WGT DAY 22 (G)** | 212.9 ± 2.361 [8] | 207.9 ± 4.984 [8] | 212.6 ± 4.013 [8] | 218.2 ± 3.260 [8] | 212.7 ± 2.666 [8] | 190.2 ± 4.381 [8]\*\* | 0.052 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 2.940 [8] | 211.5 ± 5.351 [8] | 219.7 ± 3.984 [8] | 223.2 ± 3.292 [8] | 211.2 ± 2.845 [8] | 167.0 ± 7.017 [8]\*\* | 0.002 |
| **DAY 8- DAY 1 (G)** | 18.05 ± 1.917 [8] | 16.25 ± 1.288 [8] | 17.25 ± 1.115 [8] | 18.23 ± 1.472 [8] | 16.48 ± 0.823 [8] | 19.59 ± 0.757 [8] | 0.282 |
| **DAY 15- DAY 1 (G)** | 28.71 ± 2.420 [8] | 28.29 ± 2.495 [8] | 30.65 ± 1.756 [8] | 32.14 ± 1.943 [8] | 29.75 ± 1.674 [8] | 27.55 ± 1.761 [8] | 0.780 |
| **DAY 22- DAY 1 (G)** | 40.20 ± 2.426 [8] | 42.16 ± 2.365 [8] | 41.10 ± 2.277 [8] | 45.10 ± 1.875 [8] | 40.20 ± 2.126 [8] | 18.59 ± 1.817 [8]\*\* | 0.015 |
| **DAY 29- DAY 1 (G)** | 45.14 ± 3.167 [8] | 45.73 ± 2.507 [8] | 48.20 ± 2.045 [8] | 50.11 ± 2.675 [8] | 38.65 ± 2.626 [8] | -4.63 ± 4.844 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **25 mg/kg CPS (ip x6)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 172.7 ± 2.910 [8] | 173.0 ± 2.574 [8] | 0.674 |
| **BODY WGT DAY 8 (G)** | 190.7 ± 2.817 [8] | 193.8 ± 3.572 [8] | 0.600 |
| **BODY WGT DAY 15 (G)** | 201.4 ± 2.489 [8] | 210.2 ± 5.740 [8] | 0.093 |
| **BODY WGT DAY 22 (G)** | 212.9 ± 2.361 [8] | 221.1 ± 6.080 [8] | 0.207 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 2.940 [8] | 213.6 ± 4.899 [8] | 0.600 |
| **DAY 8- DAY 1 (G)** | 18.05 ± 1.917 [8] | 20.81 ± 1.981 [8] | 0.226 |
| **DAY 15- DAY 1 (G)** | 28.71 ± 2.420 [8] | 37.15 ± 3.690 [8] | 0.093 |
| **DAY 22- DAY 1 (G)** | 40.20 ± 2.426 [8] | 48.11 ± 4.215 [8] | 0.207 |
| **DAY 29- DAY 1 (G)** | 45.14 ± 3.167 [8] | 40.58 ± 2.712 [8] | 0.345 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 4 PFDA T DEPENDENT AB RESPONSE DAY 4 IN FEMALE RATS  STUDY 2** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **IGM PFC/10^6 SP.C.** | 470.2 ± 98.36 [8] | 241.3 ± 38.12 [8] | 315.1 ± 61.98 [8] | 507.5 ± 104.8 [8] | 0.545 |
| **IGM PFC/SPLEEN 10^3** | 446.6 ± 113.6 [8] | 207.8 ± 43.02 [8] | 275.6 ± 64.69 [8] | 403.9 ± 81.23 [8] | 0.749 |
| **CELLS/SPLEEN 10^7** | 89.81 ± 5.945 [8] | 82.53 ± 6.927 [8] | 84.93 ± 4.778 [8] | 80.42 ± 3.378 [8] | 0.449 |
| **SPLEEN WEIGHT (MG)** | 627.1 ± 38.36 [8] | 603.6 ± 41.15 [8] | 571.6 ± 18.19 [8] | 557.4 ± 23.02 [8] | 0.139 |
| **BODY WEIGHT (G)** | 219.6 ± 5.304 [8] | 216.5 ± 4.833 [8] | 225.1 ± 4.891 [8] | 217.3 ± 4.638 [8] | 0.880 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **IGM PFC/10^6 SP.C.** | 470.2 ± 98.36 [8] | 1.99 ± 0.350 [8]\*\* | <.001 |
| **IGM PFC/SPLEEN 10^3** | 446.6 ± 113.6 [8] | 1.00 ± 0.000 [8]\*\* | <.001 |
| **CELLS/SPLEEN 10^7** | 89.81 ± 5.945 [8] | 14.06 ± 0.836 [8]\*\* | <.001 |
| **SPLEEN WEIGHT (MG)** | 627.1 ± 38.36 [8] | 290.5 ± 29.30 [8]\*\* | 0.001 |
| **BODY WEIGHT (G)** | 219.6 ± 5.304 [8] | 204.5 ± 2.886 [8]\* | 0.046 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01]  c: For body weight and organ weight endpoints, positive control group was compared to control using a two-sample t-test.  For other endpoints, positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 5 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 2** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 168.3 ± 3.397 [8] | 166.9 ± 1.441 [8] | 171.9 ± 2.734 [8] | 166.5 ± 2.612 [8] | 168.7 ± 3.169 [8] | 168.0 ± 2.676 [8] | 0.971 |
| **BODY WGT DAY 8 (G)** | 185.7 ± 3.103 [8] | 180.7 ± 2.807 [8] | 189.6 ± 3.264 [8] | 181.5 ± 2.540 [8] | 183.3 ± 3.160 [8] | 184.8 ± 2.159 [8] | 0.971 |
| **BODY WGT DAY 15 (G)** | 198.5 ± 3.555 [8] | 198.4 ± 3.862 [8] | 205.8 ± 4.245 [8] | 199.5 ± 3.327 [8] | 196.1 ± 3.220 [8] | 182.8 ± 3.431 [8]\* | 0.011 |
| **BODY WGT DAY 22 (G)** | 213.5 ± 3.316 [8] | 212.8 ± 2.647 [8] | 221.4 ± 3.882 [8] | 213.8 ± 3.988 [8] | 199.3 ± 3.933 [8]\* | 174.4 ± 4.893 [8]\*\* | <.001 |
| **BODY WGT DAY 29 (G)** | 219.6 ± 5.304 [8] | 216.5 ± 4.833 [8] | 225.1 ± 4.891 [8] | 217.3 ± 4.638 [8] | 198.3 ± 4.298 [8]\*\* | 158.9 ± 5.777 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 17.38 ± 1.733 [8] | 13.87 ± 1.845 [8] | 17.65 ± 2.181 [8] | 15.03 ± 1.041 [8] | 14.64 ± 1.309 [8] | 16.89 ± 1.232 [8] | 0.950 |
| **DAY 15- DAY 1 (G)** | 30.26 ± 2.921 [8] | 31.55 ± 2.988 [8] | 33.91 ± 3.808 [8] | 33.00 ± 1.972 [8] | 27.40 ± 2.149 [8] | 14.83 ± 3.335 [8]\*\* | 0.003 |
| **DAY 22- DAY 1 (G)** | 45.23 ± 2.362 [8] | 45.93 ± 2.307 [8] | 49.49 ± 3.888 [8] | 47.31 ± 2.747 [8] | 30.64 ± 1.998 [8]\*\* | 6.45 ± 4.516 [8]\*\* | <.001 |
| **DAY 29- DAY 1 (G)** | 51.30 ± 4.263 [8] | 49.68 ± 3.705 [8] | 53.18 ± 3.717 [8] | 50.78 ± 3.463 [8] | 29.63 ± 2.775 [8]\*\* | -9.05 ± 5.409 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 168.3 ± 3.397 [8] | 168.4 ± 1.832 [8] | 0.529 |
| **BODY WGT DAY 8 (G)** | 185.7 ± 3.103 [8] | 185.7 ± 2.062 [8] | 0.674 |
| **BODY WGT DAY 15 (G)** | 198.5 ± 3.555 [8] | 201.3 ± 2.592 [8] | 0.600 |
| **BODY WGT DAY 22 (G)** | 213.5 ± 3.316 [8] | 209.9 ± 2.949 [8] | 0.207 |
| **BODY WGT DAY 29 (G)** | 219.6 ± 5.304 [8] | 204.5 ± 2.886 [8]\* | 0.046 |
| **DAY 8- DAY 1 (G)** | 17.38 ± 1.733 [8] | 17.34 ± 1.729 [8] | 1.000 |
| **DAY 15- DAY 1 (G)** | 30.26 ± 2.921 [8] | 32.94 ± 1.894 [8] | 0.345 |
| **DAY 22- DAY 1 (G)** | 45.23 ± 2.362 [8] | 41.54 ± 1.705 [8] | 0.141 |
| **DAY 29- DAY 1 (G)** | 51.30 ± 4.263 [8] | 36.14 ± 1.905 [8]\*\* | 0.016 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 6 PFDA DELAYED TYPE HYPERSENSITIVITY IN FEMALE RATS  STUDY 3** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **24 HR (MM X 100)** | 117.1 ± 13.21 [8] | 77.38 ± 17.20 [8] | 86.50 ± 14.52 [8] | 86.19 ± 14.16 [8] | 0.144 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **24 HR (MM X 100)** | 117.1 ± 13.21 [8] | 27.94 ± 4.028 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **Challenge Only** | **Trendc** |
| --- | --- | --- | --- |
| **24 HR (MM X 100)** | 117.1 ± 13.21 [8] | 5.81 ± 4.186 [8]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 7 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 3** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 170.7 ± 2.227 [8] | 170.8 ± 2.053 [8] | 173.7 ± 2.642 [8] | 168.5 ± 2.689 [8] | 171.0 ± 1.987 [8] | 169.4 ± 2.772 [8] | 0.576 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.891 [8] | 187.7 ± 2.568 [8] | 188.2 ± 2.227 [8] | 182.2 ± 3.175 [8] | 190.2 ± 2.405 [8] | 184.4 ± 3.357 [8] | 0.800 |
| **BODY WGT DAY 15 (G)** | 201.4 ± 3.470 [8] | 202.4 ± 2.836 [8] | 206.4 ± 2.308 [8] | 201.9 ± 3.970 [8] | 205.9 ± 3.158 [8] | 194.1 ± 4.518 [8] | 0.639 |
| **BODY WGT DAY 22 (G)** | 211.3 ± 3.663 [8] | 212.7 ± 3.647 [8] | 213.1 ± 4.162 [8] | 205.9 ± 4.913 [8] | 207.5 ± 3.432 [8] | 177.5 ± 7.977 [8]\*\* | <.001 |
| **BODY WGT DAY 29 (G)** | 221.3 ± 4.448 [8] | 218.2 ± 3.131 [8] | 226.3 ± 4.394 [8] | 212.5 ± 3.969 [8] | 206.6 ± 4.226 [8]\* | 168.8 ± 4.796 [6]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 16.44 ± 1.307 [8] | 16.90 ± 1.717 [8] | 14.44 ± 1.408 [8] | 13.65 ± 1.506 [8] | 19.24 ± 1.493 [8] | 14.94 ± 1.249 [8] | 0.773 |
| **DAY 15- DAY 1 (G)** | 30.68 ± 1.613 [8] | 31.69 ± 2.249 [8] | 32.69 ± 1.296 [8] | 33.39 ± 2.612 [8] | 34.94 ± 1.519 [8] | 24.61 ± 2.851 [8] | 0.759 |
| **DAY 22- DAY 1 (G)** | 40.58 ± 1.658 [8] | 41.90 ± 3.393 [8] | 39.41 ± 2.539 [8] | 37.39 ± 2.812 [8] | 36.53 ± 2.008 [8] | 8.03 ± 6.384 [8]\*\* | <.001 |
| **DAY 29- DAY 1 (G)** | 50.56 ± 2.606 [8] | 47.49 ± 2.434 [8] | 52.56 ± 2.527 [8] | 43.99 ± 2.607 [8] | 35.68 ± 2.882 [8]\*\* | -2.65 ± 3.373 [6]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 170.7 ± 2.227 [8] | 174.3 ± 3.613 [8] | 0.674 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.891 [8] | 194.9 ± 5.495 [8] | 0.294 |
| **BODY WGT DAY 15 (G)** | 201.4 ± 3.470 [8] | 210.5 ± 3.753 [8] | 0.074 |
| **BODY WGT DAY 22 (G)** | 211.3 ± 3.663 [8] | 219.2 ± 4.405 [8] | 0.172 |
| **BODY WGT DAY 29 (G)** | 221.3 ± 4.448 [8] | 212.8 ± 4.828 [8] | 0.141 |
| **DAY 8- DAY 1 (G)** | 16.44 ± 1.307 [8] | 20.66 ± 1.990 [8] | 0.141 |
| **DAY 15- DAY 1 (G)** | 30.68 ± 1.613 [8] | 36.23 ± 1.406 [8]\* | 0.036 |
| **DAY 22- DAY 1 (G)** | 40.58 ± 1.658 [8] | 44.94 ± 2.007 [8] | 0.083 |
| **DAY 29- DAY 1 (G)** | 50.56 ± 2.606 [8] | 38.49 ± 1.895 [8]\*\* | 0.003 |

| **TABLE 7 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **Challenge Only** | **Trendc** |
| **BODY WGT DAY 1 (G)** | 170.7 ± 2.227 [8] | 172.4 ± 1.288 [8] | 0.431 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.891 [8] | 192.0 ± 2.150 [8] | 0.208 |
| **BODY WGT DAY 15 (G)** | 201.4 ± 3.470 [8] | 213.9 ± 3.263 [8]\* | 0.027 |
| **BODY WGT DAY 22 (G)** | 211.3 ± 3.663 [8] | 221.5 ± 3.115 [8] | 0.066 |
| **BODY WGT DAY 29 (G)** | 221.3 ± 4.448 [8] | 228.3 ± 3.627 [8] | 0.248 |
| **DAY 8- DAY 1 (G)** | 16.44 ± 1.307 [8] | 19.56 ± 1.058 [8] | 0.074 |
| **DAY 15- DAY 1 (G)** | 30.68 ± 1.613 [8] | 41.46 ± 2.320 [8]\*\* | 0.003 |
| **DAY 22- DAY 1 (G)** | 40.58 ± 1.658 [8] | 49.13 ± 2.271 [8]\*\* | 0.021 |
| **DAY 29- DAY 1 (G)** | 50.56 ± 2.606 [8] | 55.88 ± 3.012 [8] | 0.248 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 8 PFDA KEYHOLE LIMPET HEMOCYANIN IN FEMALE RATS  STUDY 4** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **SERUM ANTI-KLH IGM (UG/ML)** | 14.90 ± 4.004 [8] | 23.52 ± 12.73 [8] | 21.01 ± 5.957 [8] | 14.17 ± 2.713 [8] | 0.502 |

| **Parametera** | **Vehicle Control** | **25 mg/kg CPS (ip x6)** | **Trendc** |
| --- | --- | --- | --- |
| **SERUM ANTI-KLH IGM (UG/ML)** | 14.90 ± 4.004 [8] | 0.12 ± 0.027 [8]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 9 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 4** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 169.6 ± 1.751 [8] | 172.5 ± 1.670 [8] | 171.8 ± 1.985 [8] | 169.7 ± 1.808 [8] | 168.9 ± 2.063 [8] | 168.8 ± 2.029 [8] | 0.237 |
| **BODY WGT DAY 8 (G)** | 183.3 ± 2.398 [8] | 186.6 ± 1.885 [8] | 184.9 ± 3.077 [8] | 183.5 ± 1.766 [8] | 184.7 ± 3.364 [8] | 181.6 ± 2.782 [8] | 0.230 |
| **BODY WGT DAY 15 (G)** | 196.2 ± 2.376 [8] | 202.3 ± 3.021 [8] | 202.1 ± 2.662 [8] | 195.7 ± 2.074 [8] | 194.2 ± 3.888 [8] | 181.7 ± 4.014 [8]\*\* | 0.005 |
| **BODY WGT DAY 22 (G)** | 208.0 ± 2.626 [8] | 213.9 ± 2.787 [8] | 214.4 ± 2.994 [8] | 206.9 ± 2.509 [8] | 200.7 ± 3.401 [8] | 174.7 ± 4.335 [8]\*\* | <.001 |
| **BODY WGT DAY 29 (G)** | 214.8 ± 3.777 [8] | 219.7 ± 2.963 [8] | 221.0 ± 3.819 [8] | 214.1 ± 2.653 [8] | 201.0 ± 3.733 [8]\* | 158.5 ± 5.370 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 13.76 ± 1.906 [8] | 14.14 ± 1.435 [8] | 13.08 ± 1.442 [8] | 13.76 ± 1.254 [8] | 15.75 ± 1.437 [8] | 12.81 ± 1.641 [8] | 0.935 |
| **DAY 15- DAY 1 (G)** | 26.60 ± 1.839 [8] | 29.84 ± 2.096 [8] | 30.29 ± 1.861 [8] | 25.99 ± 1.726 [8] | 25.31 ± 2.079 [8] | 12.84 ± 2.526 [8]\*\* | 0.001 |
| **DAY 22- DAY 1 (G)** | 38.44 ± 1.212 [8] | 41.41 ± 2.100 [8] | 42.58 ± 2.204 [8] | 37.20 ± 2.439 [8] | 31.76 ± 2.240 [8] | 5.85 ± 2.940 [8]\*\* | <.001 |
| **DAY 29- DAY 1 (G)** | 45.24 ± 2.592 [8] | 47.24 ± 2.686 [8] | 49.23 ± 2.645 [8] | 44.36 ± 2.400 [8] | 32.08 ± 3.107 [8]\*\* | -10.3 ± 4.366 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **25 mg/kg CPS (ip x6)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 169.6 ± 1.751 [8] | 168.6 ± 2.154 [8] | 0.753 |
| **BODY WGT DAY 8 (G)** | 183.3 ± 2.398 [8] | 183.8 ± 3.142 [8] | 0.636 |
| **BODY WGT DAY 15 (G)** | 196.2 ± 2.376 [8] | 198.3 ± 4.476 [8] | 0.958 |
| **BODY WGT DAY 22 (G)** | 208.0 ± 2.626 [8] | 208.2 ± 3.972 [8] | 0.916 |
| **BODY WGT DAY 29 (G)** | 214.8 ± 3.777 [8] | 205.0 ± 3.296 [8] | 0.115 |
| **DAY 8- DAY 1 (G)** | 13.76 ± 1.906 [8] | 15.21 ± 1.855 [8] | 0.713 |
| **DAY 15- DAY 1 (G)** | 26.60 ± 1.839 [8] | 29.69 ± 3.004 [8] | 0.462 |
| **DAY 22- DAY 1 (G)** | 38.44 ± 1.212 [8] | 39.59 ± 2.865 [8] | 0.636 |
| **DAY 29- DAY 1 (G)** | 45.24 ± 2.592 [8] | 36.39 ± 2.182 [8]\* | 0.046 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 10 PFDA T DEPENDENT AB RESPONSE DAY 4 IN FEMALE RATS  STUDY 5** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **IGM PFC/10^6 SP.C.** | 627.6 ± 155.0 [8] | 619.2 ± 155.9 [8] | 578.0 ± 88.36 [8] | 502.6 ± 133.2 [8] | 0.347 |
| **IGM PFC/SPLEEN 10^3** | 546.4 ± 124.8 [8] | 512.6 ± 126.8 [8] | 487.9 ± 81.61 [8] | 417.8 ± 112.4 [8] | 0.246 |
| **CELLS/SPLEEN 10^7** | 89.45 ± 2.312 [8] | 80.47 ± 3.399 [8] | 82.22 ± 4.090 [8] | 83.47 ± 2.741 [8] | 0.290 |
| **SPLEEN WEIGHT (MG)** | 622.0 ± 12.21 [8] | 604.0 ± 32.77 [8] | 563.1 ± 14.85 [8] | 572.0 ± 20.33 [8] | 0.022 |
| **BODY WEIGHT (G)** | 216.1 ± 3.067 [8] | 219.4 ± 4.981 [8] | 215.1 ± 3.076 [8] | 220.2 ± 3.499 [8] | 0.801 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **IGM PFC/10^6 SP.C.** | 627.6 ± 155.0 [8] | 2.65 ± 0.477 [8]\*\* | 0.002 |
| **IGM PFC/SPLEEN 10^3** | 546.4 ± 124.8 [8] | 1.00 ± 0.000 [8]\*\* | <.001 |
| **CELLS/SPLEEN 10^7** | 89.45 ± 2.312 [8] | 13.01 ± 0.772 [8]\*\* | <.001 |
| **SPLEEN WEIGHT (MG)** | 622.0 ± 12.21 [8] | 272.9 ± 8.539 [8]\*\* | <.001 |
| **BODY WEIGHT (G)** | 216.1 ± 3.067 [8] | 203.6 ± 3.542 [8]\* | 0.021 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01]  c: For body weight and organ weight endpoints, positive control group was compared to control using a two-sample t-test.  For other endpoints, positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 11 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 5** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 171.5 ± 2.243 [8] | 173.4 ± 2.587 [8] | 170.6 ± 2.347 [8] | 169.9 ± 2.934 [8] | 171.7 ± 1.846 [8] | 168.0 ± 2.073 [8] | 0.216 |
| **BODY WGT DAY 8 (G)** | 187.0 ± 2.794 [8] | 192.0 ± 4.113 [8] | 181.8 ± 2.186 [8] | 186.1 ± 3.036 [8] | 189.7 ± 2.301 [8] | 181.4 ± 1.541 [8] | 0.299 |
| **BODY WGT DAY 15 (G)** | 202.1 ± 3.387 [8] | 203.0 ± 3.650 [8] | 194.8 ± 1.787 [8] | 202.1 ± 3.613 [8] | 203.6 ± 1.916 [8] | 186.9 ± 1.865 [8]\*\* | 0.045 |
| **BODY WGT DAY 22 (G)** | 210.4 ± 2.786 [8] | 213.7 ± 4.289 [8] | 207.2 ± 2.563 [8] | 214.0 ± 3.385 [8] | 212.2 ± 1.792 [8] | 180.4 ± 1.608 [8]\*\* | 0.009 |
| **BODY WGT DAY 29 (G)** | 216.1 ± 3.067 [8] | 219.4 ± 4.981 [8] | 215.1 ± 3.076 [8] | 220.2 ± 3.499 [8] | 212.9 ± 2.068 [8] | 162.2 ± 2.104 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 15.50 ± 1.648 [8] | 18.61 ± 2.821 [8] | 11.15 ± 0.808 [8] | 16.16 ± 1.263 [8] | 18.04 ± 1.630 [8] | 13.38 ± 1.379 [8] | 0.800 |
| **DAY 15- DAY 1 (G)** | 30.64 ± 2.124 [8] | 29.55 ± 2.203 [8] | 24.16 ± 1.325 [8]\* | 32.16 ± 1.482 [8] | 31.85 ± 1.186 [8] | 18.86 ± 1.151 [8]\*\* | 0.070 |
| **DAY 22- DAY 1 (G)** | 38.96 ± 1.467 [8] | 40.31 ± 2.761 [8] | 36.54 ± 1.323 [8] | 44.10 ± 1.822 [8] | 40.46 ± 1.593 [8] | 12.34 ± 1.759 [8]\*\* | 0.042 |
| **DAY 29- DAY 1 (G)** | 44.61 ± 1.874 [8] | 46.01 ± 3.341 [8] | 44.43 ± 1.653 [8] | 50.26 ± 2.105 [8] | 41.21 ± 2.253 [8] | -5.83 ± 3.476 [8]\*\* | 0.004 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 171.5 ± 2.243 [8] | 172.2 ± 1.975 [8] | 0.916 |
| **BODY WGT DAY 8 (G)** | 187.0 ± 2.794 [8] | 190.3 ± 2.053 [8] | 0.462 |
| **BODY WGT DAY 15 (G)** | 202.1 ± 3.387 [8] | 206.2 ± 2.480 [8] | 0.462 |
| **BODY WGT DAY 22 (G)** | 210.4 ± 2.786 [8] | 215.1 ± 2.616 [8] | 0.431 |
| **BODY WGT DAY 29 (G)** | 216.1 ± 3.067 [8] | 203.6 ± 3.542 [8]\* | 0.021 |
| **DAY 8- DAY 1 (G)** | 15.50 ± 1.648 [8] | 18.08 ± 1.178 [8] | 0.189 |
| **DAY 15- DAY 1 (G)** | 30.64 ± 2.124 [8] | 33.98 ± 1.477 [8] | 0.115 |
| **DAY 22- DAY 1 (G)** | 38.96 ± 1.467 [8] | 42.93 ± 1.332 [8] | 0.093 |
| **DAY 29- DAY 1 (G)** | 44.61 ± 1.874 [8] | 31.44 ± 2.726 [8]\*\* | 0.006 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 12 PFDA ANTI CD3 PROLIFERATION IN FEMALE RATS  STUDY 6** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **TOTAL CELLS(X10E7)** | 82.49 ± 3.795 [8] | 82.92 ± 5.100 [8] | 67.68 ± 2.985 [8]\* | 63.90 ± 2.232 [8]\*\* | <.001 |
| **RESPONDERS** | 7011 ± 881.4 [8] | 8721 ± 1533 [8] | 10194 ± 2306 [8] | 9483 ± 2759 [8] | 0.460 |
| **RESPONDERS + ANTI-CD3** | 151E3 ± 20246 [8] | 159E3 ± 18947 [8] | 176E3 ± 31930 [8] | 122E3 ± 32032 [8] | 0.662 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **TOTAL CELLS(X10E7)** | 82.49 ± 3.795 [8] | 10.73 ± 0.820 [8]\*\* | <.001 |
| **RESPONDERS** | 7011 ± 881.4 [8] | 3624 ± 1329 [8] | 0.059 |
| **RESPONDERS + ANTI-CD3** | 151E3 ± 20246 [8] | 60562 ± 25597 [8]\* | 0.021 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 13 PFDA DNA SYNTHESIS IN FEMALE RATS  STUDY 6** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **TOTAL CELLS (X 10^6)** | 62.41 ± 5.246 [8] | 69.21 ± 5.181 [8] | 62.85 ± 4.887 [8] | 62.91 ± 3.988 [8] | 0.762 |
| **DNA SYNTHESIS (CPM)** | 77119 ± 5629 [8] | 80170 ± 10099 [8] | 86032 ± 5353 [8] | 80572 ± 6324 [8] | 0.401 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **TOTAL CELLS (X 10^6)** | 62.41 ± 5.246 [8] | 8.88 ± 1.358 [8]\*\* | <.001 |
| **DNA SYNTHESIS (CPM)** | 77119 ± 5629 [8] | 5189 ± 1293 [8]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 14 PFDA BONE MARROW IN FEMALE RATS  STUDY 6** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **CELLS/FEMUR X10^6** | 62.41 ± 5.246 [8] | 69.21 ± 5.181 [8] | 62.85 ± 4.887 [8] | 62.91 ± 3.988 [8] | 0.762 |
| **CFU-GM/10^5 CELLS** | 117.4 ± 5.677 [7] | 105.3 ± 5.431 [8] | 113.4 ± 5.976 [8] | 109.6 ± 2.070 [8] | 0.685 |
| **CFU-GM/FEMUR X10^4** | 7.20 ± 0.725 [7] | 7.29 ± 0.669 [8] | 7.21 ± 0.814 [8] | 6.92 ± 0.544 [8] | 0.725 |
| **CFU-M/10^5 CELLS** | 178.1 ± 4.026 [7] | 172.3 ± 9.029 [8] | 165.1 ± 5.792 [8] | 168.1 ± 5.680 [8] | 0.198 |
| **CFU-M/FEMUR X10^4** | 10.98 ± 1.001 [7] | 11.73 ± 0.762 [8] | 10.37 ± 0.936 [8] | 10.42 ± 0.404 [8] | 0.307 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **CELLS/FEMUR X10^6** | 62.41 ± 5.246 [8] | 8.88 ± 1.358 [8]\*\* | <.001 |
| **CFU-GM/10^5 CELLS** | 117.4 ± 5.677 [7] | 8.75 ± 2.717 [8]\*\* | 0.001 |
| **CFU-GM/FEMUR X10^4** | 7.20 ± 0.725 [7] | 0.07 ± 0.023 [8]\*\* | 0.001 |
| **CFU-M/10^5 CELLS** | 178.1 ± 4.026 [7] | 7.50 ± 2.360 [8]\*\* | 0.001 |
| **CFU-M/FEMUR X10^4** | 10.98 ± 1.001 [7] | 0.07 ± 0.029 [8]\*\* | 0.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 15 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 6** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 175.2 ± 2.537 [8] | 175.1 ± 4.131 [8] | 175.5 ± 3.228 [8] | 175.2 ± 3.271 [8] | 174.3 ± 2.977 [8] | 174.8 ± 2.712 [8] | 0.786 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.492 [8] | 187.7 ± 3.475 [8] | 185.0 ± 3.016 [8] | 186.7 ± 3.300 [8] | 189.6 ± 4.137 [8] | 187.1 ± 2.809 [8] | 0.745 |
| **BODY WGT DAY 15 (G)** | 197.4 ± 2.722 [8] | 198.3 ± 4.652 [8] | 195.7 ± 2.865 [8] | 197.5 ± 3.751 [8] | 200.7 ± 4.020 [8] | 191.0 ± 3.228 [8] | 0.348 |
| **BODY WGT DAY 22 (G)** | 207.6 ± 2.434 [8] | 210.2 ± 3.934 [8] | 205.1 ± 3.028 [8] | 208.8 ± 3.660 [8] | 208.8 ± 5.589 [8] | 186.2 ± 3.804 [8]\*\* | 0.007 |
| **BODY WGT DAY 29 (G)** | 214.1 ± 2.778 [8] | 214.9 ± 4.957 [8] | 210.3 ± 3.669 [8] | 211.2 ± 4.214 [8] | 208.3 ± 6.255 [8] | 171.5 ± 4.589 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 12.06 ± 1.242 [8] | 12.59 ± 2.093 [8] | 9.50 ± 1.785 [8] | 11.51 ± 1.663 [8] | 15.30 ± 1.730 [8] | 12.29 ± 2.258 [8] | 0.259 |
| **DAY 15- DAY 1 (G)** | 22.19 ± 0.970 [8] | 23.16 ± 1.877 [8] | 20.17 ± 2.548 [8] | 22.35 ± 2.474 [8] | 26.45 ± 1.551 [8] | 16.20 ± 3.925 [8] | 0.793 |
| **DAY 22- DAY 1 (G)** | 32.40 ± 0.998 [8] | 35.11 ± 2.081 [8] | 29.65 ± 2.668 [8] | 33.59 ± 2.464 [8] | 34.50 ± 2.999 [8] | 11.44 ± 3.935 [8]\*\* | 0.028 |
| **DAY 29- DAY 1 (G)** | 38.90 ± 0.779 [8] | 39.75 ± 2.485 [8] | 34.80 ± 2.960 [8] | 35.99 ± 2.873 [8] | 34.00 ± 4.184 [8] | -3.25 ± 4.096 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 175.2 ± 2.537 [8] | 172.6 ± 3.345 [8] | 0.248 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.492 [8] | 183.5 ± 2.433 [8] | 0.172 |
| **BODY WGT DAY 15 (G)** | 197.4 ± 2.722 [8] | 194.2 ± 2.987 [8] | 0.529 |
| **BODY WGT DAY 22 (G)** | 207.6 ± 2.434 [8] | 201.5 ± 3.015 [8] | 0.208 |
| **BODY WGT DAY 29 (G)** | 214.1 ± 2.778 [8] | 191.5 ± 4.024 [8]\*\* | 0.002 |
| **DAY 8- DAY 1 (G)** | 12.06 ± 1.242 [8] | 10.91 ± 1.758 [8] | 0.713 |
| **DAY 15- DAY 1 (G)** | 22.19 ± 0.970 [8] | 21.61 ± 2.082 [8] | 0.462 |
| **DAY 22- DAY 1 (G)** | 32.40 ± 0.998 [8] | 28.96 ± 2.704 [8] | 0.318 |
| **DAY 29- DAY 1 (G)** | 38.90 ± 0.779 [8] | 18.92 ± 2.816 [8]\*\* | <.001 |

| **TABLE 15 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **1/10 AAGM1 (iv x 1)** | **Trendc** |
| **BODY WGT DAY 1 (G)** | 175.2 ± 2.537 [8] | 172.1 ± 2.166 [8] | 0.293 |
| **BODY WGT DAY 8 (G)** | 187.2 ± 2.492 [8] | 186.6 ± 2.040 [8] | 0.528 |
| **BODY WGT DAY 15 (G)** | 197.4 ± 2.722 [8] | 200.1 ± 3.263 [8] | 0.636 |
| **BODY WGT DAY 22 (G)** | 207.6 ± 2.434 [8] | 211.0 ± 3.582 [8] | 0.172 |
| **BODY WGT DAY 29 (G)** | 214.1 ± 2.778 [8] | 216.7 ± 4.895 [8] | 0.600 |
| **DAY 8- DAY 1 (G)** | 12.06 ± 1.242 [8] | 14.47 ± 1.189 [8] | 0.189 |
| **DAY 15- DAY 1 (G)** | 22.19 ± 0.970 [8] | 28.04 ± 2.558 [8] | 0.021 |
| **DAY 22- DAY 1 (G)** | 32.40 ± 0.998 [8] | 38.96 ± 2.468 [8]\* | 0.059 |
| **DAY 29- DAY 1 (G)** | 38.90 ± 0.779 [8] | 44.61 ± 3.628 [8] | 0.401 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 16 PFDA MONONUCLEAR PHAGOCYTIC SYSTEM IN FEMALE RATS  STUDY 7** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **HALF LIFE** | 11.23 ± 1.708 [8] | 11.76 ± 2.549 [8] | 23.60 ± 10.43 [8] | 15.32 ± 2.554 [8] | 0.158 |
| **BODY WGT (G)** | 214.6 ± 2.580 [8] | 213.0 ± 5.367 [8] | 218.9 ± 3.271 [8] | 217.7 ± 3.623 [8] | 0.401 |
| **LIVER WGT (MG)** | 7347 ± 234.8 [8] | 8052 ± 330.0 [8] | 8467 ± 298.1 [8]\*\* | 9124 ± 158.5 [8]\*\* | <.001 |
| **SPLEEN WGT (MG)** | 575.3 ± 21.36 [8] | 594.5 ± 29.98 [8] | 577.1 ± 30.72 [8] | 509.8 ± 24.86 [8] | 0.103 |
| **LUNG WGT (MG)** | 1485 ± 65.21 [8] | 1422 ± 58.89 [8] | 1423 ± 45.71 [8] | 1518 ± 57.98 [8] | 0.762 |
| **THYMUS WGT (MG)** | 245.4 ± 22.96 [8] | 277.9 ± 20.40 [8] | 301.5 ± 30.55 [8] | 276.3 ± 19.76 [8] | 0.239 |
| **KIDNEY WGT (MG)** | 1700 ± 50.56 [8] | 1732 ± 66.41 [8] | 1734 ± 43.69 [8] | 1780 ± 50.86 [8] | 0.321 |
| **% UPTAKE LIVER** | 23.68 ± 1.342 [8] | 22.31 ± 1.367 [8] | 20.41 ± 2.117 [8] | 17.74 ± 2.428 [8] | 0.029 |
| **LIVER CTS/LIVER WGT** | 263.6 ± 15.04 [8] | 224.8 ± 11.98 [8] | 200.6 ± 19.32 [8]\* | 161.2 ± 22.22 [8]\*\* | <.001 |
| **% UPTAKE SPLEEN** | 1.85 ± 0.265 [8] | 3.10 ± 0.797 [8] | 2.51 ± 0.413 [8] | 2.31 ± 0.427 [8] | 0.460 |
| **SPLEEN CTS/SPLEEN WGT** | 263.2 ± 36.81 [8] | 435.4 ± 117.9 [8] | 360.1 ± 57.37 [8] | 387.1 ± 74.73 [8] | 0.214 |
| **% UPTAKE LUNG** | 0.18 ± 0.030 [8] | 0.28 ± 0.078 [8] | 0.21 ± 0.063 [8] | 0.32 ± 0.049 [8] | 0.075 |
| **LUNG CTS/LUNG WGT** | 9.53 ± 1.496 [8] | 16.26 ± 4.733 [8] | 12.10 ± 3.301 [8] | 17.75 ± 3.139 [8] | 0.075 |
| **% UPTAKE THYMUS** | 0.00 ± 0.001 [8] | 0.01 ± 0.002 [8] | 0.00 ± 0.001 [8] | 0.01 ± 0.002 [8]\* | 0.010 |
| **THUMUS CTS/THYMUS WGT** | 1.09 ± 0.174 [8] | 1.44 ± 0.468 [8] | 1.30 ± 0.343 [8] | 2.60 ± 0.426 [8]\* | 0.029 |
| **% UPTAKE KIDNEY** | 1.14 ± 0.149 [8] | 0.80 ± 0.178 [8] | 1.52 ± 0.447 [8] | 1.79 ± 0.197 [8] | 0.024 |
| **KIDNEY CTS/KIDNEY WGT** | 54.82 ± 7.214 [8] | 37.62 ± 8.354 [8] | 70.57 ± 17.77 [8] | 82.60 ± 8.114 [8] | 0.031 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 16 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **50 mg/kg MVE (iv x 1)** | **Trendc** |
| **HALF LIFE** | 11.23 ± 1.708 [8] | 80.13 ± 20.25 [7]\*\* | 0.001 |
| **BODY WGT (G)** | 214.6 ± 2.580 [8] | 204.1 ± 3.563 [7]\* | 0.082 |
| **LIVER WGT (MG)** | 7347 ± 234.8 [8] | 8081 ± 243.4 [7]\* | 0.037 |
| **SPLEEN WGT (MG)** | 575.3 ± 21.36 [8] | 456.0 ± 20.78 [7]\*\* | 0.004 |
| **LUNG WGT (MG)** | 1485 ± 65.21 [8] | 1497 ± 50.09 [7] | 0.817 |
| **THYMUS WGT (MG)** | 245.4 ± 22.96 [8] | 255.6 ± 6.701 [7] | 0.728 |
| **KIDNEY WGT (MG)** | 1700 ± 50.56 [8] | 1727 ± 48.16 [7] | 0.487 |
| **% UPTAKE LIVER** | 23.68 ± 1.342 [8] | 3.88 ± 0.253 [7]\*\* | 0.001 |
| **LIVER CTS/LIVER WGT** | 263.6 ± 15.04 [8] | 37.13 ± 1.944 [7]\*\* | 0.001 |
| **% UPTAKE SPLEEN** | 1.85 ± 0.265 [8] | 1.34 ± 0.208 [7] | 0.132 |
| **SPLEEN CTS/SPLEEN WGT** | 263.2 ± 36.81 [8] | 232.0 ± 36.94 [7] | 0.487 |
| **% UPTAKE LUNG** | 0.18 ± 0.030 [8] | 1.56 ± 0.142 [7]\*\* | 0.001 |
| **LUNG CTS/LUNG WGT** | 9.53 ± 1.496 [8] | 80.86 ± 6.125 [7]\*\* | 0.001 |
| **% UPTAKE THYMUS** | 0.00 ± 0.001 [8] | 0.03 ± 0.010 [7]\* | 0.001 |
| **THUMUS CTS/THYMUS WGT** | 1.09 ± 0.174 [8] | 9.49 ± 3.157 [7]\* | 0.001 |
| **% UPTAKE KIDNEY** | 1.14 ± 0.149 [8] | 1.20 ± 0.232 [7] | 0.908 |
| **KIDNEY CTS/KIDNEY WGT** | 54.82 ± 7.214 [8] | 53.20 ± 8.886 [7] | 0.817 |

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| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01]  c: For body weight and organ weight endpoints, positive control group was compared to control using a two-sample t-test.  For other endpoints, positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 17 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 174.1 ± 1.871 [8] | 174.4 ± 1.597 [8] | 173.7 ± 1.444 [8] | 174.7 ± 2.413 [8] | 173.9 ± 2.058 [8] | 174.1 ± 2.681 [8] | 0.569 |
| **BODY WGT DAY 8 (G)** | 188.6 ± 1.943 [8] | 185.5 ± 2.603 [8] | 188.9 ± 1.260 [8] | 190.5 ± 2.997 [8] | 188.0 ± 2.610 [8] | 190.5 ± 3.750 [8] | 0.698 |
| **BODY WGT DAY 15 (G)** | 198.8 ± 2.506 [8] | 194.0 ± 3.801 [8] | 198.2 ± 2.170 [8] | 201.2 ± 2.338 [8] | 198.5 ± 2.815 [8] | 194.0 ± 4.866 [8] | 0.516 |
| **BODY WGT DAY 22 (G)** | 211.1 ± 2.437 [8] | 203.9 ± 4.521 [8] | 208.1 ± 2.168 [8] | 211.3 ± 3.291 [8] | 203.5 ± 3.247 [8] | 189.2 ± 4.530 [8]\*\* | 0.002 |
| **BODY WGT DAY 29 (G)** | 214.6 ± 2.580 [8] | 213.0 ± 5.367 [8] | 218.9 ± 3.271 [8] | 217.7 ± 3.623 [8] | 201.4 ± 3.385 [8]\* | 180.7 ± 5.302 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 14.50 ± 1.313 [8] | 11.13 ± 1.412 [8] | 15.23 ± 1.208 [8] | 15.79 ± 1.242 [8] | 14.15 ± 2.207 [8] | 16.44 ± 1.284 [8] | 0.200 |
| **DAY 15- DAY 1 (G)** | 24.69 ± 2.039 [8] | 19.61 ± 2.765 [8] | 24.49 ± 1.785 [8] | 26.50 ± 1.055 [8] | 24.59 ± 2.649 [8] | 19.88 ± 2.517 [8] | 0.600 |
| **DAY 22- DAY 1 (G)** | 36.96 ± 1.622 [8] | 29.55 ± 3.385 [8] | 34.43 ± 1.923 [8] | 36.61 ± 1.607 [8] | 29.64 ± 2.164 [8]\* | 15.07 ± 2.574 [8]\*\* | <.001 |
| **DAY 29- DAY 1 (G)** | 40.45 ± 2.046 [8] | 38.65 ± 4.017 [8] | 45.24 ± 3.073 [8] | 43.04 ± 1.962 [8] | 27.50 ± 3.438 [8]\*\* | 6.58 ± 3.638 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg MVE (iv x 1)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 174.1 ± 1.871 [8] | 175.4 ± 1.828 [8] | 0.834 |
| **BODY WGT DAY 8 (G)** | 188.6 ± 1.943 [8] | 191.0 ± 2.410 [8] | 0.834 |
| **BODY WGT DAY 15 (G)** | 198.8 ± 2.506 [8] | 201.9 ± 2.137 [8] | 0.345 |
| **BODY WGT DAY 22 (G)** | 211.1 ± 2.437 [8] | 213.0 ± 2.013 [8] | 0.713 |
| **BODY WGT DAY 29 (G)** | 214.6 ± 2.580 [8] | 204.4 ± 3.101 [8]\* | 0.059 |
| **DAY 8- DAY 1 (G)** | 14.50 ± 1.313 [8] | 15.61 ± 2.016 [8] | 0.958 |
| **DAY 15- DAY 1 (G)** | 24.69 ± 2.039 [8] | 26.45 ± 1.905 [8] | 0.600 |
| **DAY 22- DAY 1 (G)** | 36.96 ± 1.622 [8] | 37.60 ± 2.157 [8] | 0.752 |
| **DAY 29- DAY 1 (G)** | 40.45 ± 2.046 [8] | 28.99 ± 2.768 [8]\*\* | 0.012 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 18 PFDA ABSOLUTE SURFACE MARKERS IN FEMALE RATS  STUDY 8** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **SPL CELL# X10^7** | 80.06 ± 4.154 [8] | 69.50 ± 3.097 [8] | 81.34 ± 6.269 [8] | 73.04 ± 3.294 [8] | 0.523 |
| **ABSOL CD45+** | 402.8 ± 23.79 [8] | 336.1 ± 18.91 [8] | 407.5 ± 45.71 [8] | 363.7 ± 16.58 [8] | 0.662 |
| **ABSOL CD5+** | 248.5 ± 14.51 [8] | 218.4 ± 11.25 [8] | 258.0 ± 12.39 [8] | 235.4 ± 10.19 [8] | 0.973 |
| **ABSOL CD4+CD5+** | 155.2 ± 11.48 [8] | 137.8 ± 8.160 [8] | 157.4 ± 9.123 [8] | 149.8 ± 9.045 [8] | 0.893 |
| **ABSOL CD8+CD5+** | 88.11 ± 6.885 [8] | 77.41 ± 6.818 [8] | 95.26 ± 7.100 [8] | 84.55 ± 6.154 [8] | 0.946 |
| **ABSOL NK+CD8+** | 27.33 ± 1.480 [8] | 27.18 ± 1.329 [8] | 27.46 ± 1.544 [8] | 24.21 ± 1.039 [8] | 0.173 |
| **ABSOL MACSUBSET+** | 44.03 ± 2.572 [8] | 38.64 ± 1.542 [8] | 45.70 ± 4.122 [8] | 43.15 ± 3.242 [8] | 0.853 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **SPL CELL# X10^7** | 80.06 ± 4.154 [8] | 13.57 ± 0.807 [8]\*\* | <.001 |
| **ABSOL CD45+** | 402.8 ± 23.79 [8] | 13.84 ± 1.744 [8]\*\* | <.001 |
| **ABSOL CD5+** | 248.5 ± 14.51 [8] | 84.33 ± 7.226 [8]\*\* | <.001 |
| **ABSOL CD4+CD5+** | 155.2 ± 11.48 [8] | 33.43 ± 3.339 [8]\*\* | <.001 |
| **ABSOL CD8+CD5+** | 88.11 ± 6.885 [8] | 47.11 ± 5.130 [8]\*\* | 0.002 |
| **ABSOL MACSUBSET+** | 44.03 ± 2.572 [8] | 13.04 ± 1.222 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **1/10 AAGM1 (iv x 1)** | **Trendc** |
| --- | --- | --- | --- |
| **SPL CELL# X10^7** | 80.06 ± 4.154 [8] | 66.89 ± 3.039 [8]\* | 0.012 |
| **ABSOL NK+CD8+** | 27.33 ± 1.480 [8] | 2.23 ± 0.750 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 19 PFDA % SURFACE MARKERS IN FEMALE RATS  STUDY 8** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **%CD45+** | 50.25 ± 0.904 [8] | 48.25 ± 1.135 [8] | 49.43 ± 1.479 [8] | 49.80 ± 0.429 [8] | 0.545 |
| **%CD5+** | 30.98 ± 0.469 [8] | 31.48 ± 0.976 [8] | 32.13 ± 0.809 [8] | 32.28 ± 0.531 [8] | 0.114 |
| **%CD4+CD5+** | 19.26 ± 0.748 [8] | 19.79 ± 0.560 [8] | 19.54 ± 0.601 [8] | 20.49 ± 0.739 [8] | 0.329 |
| **%CD8+CD5+** | 11.00 ± 0.664 [8] | 11.18 ± 0.965 [8] | 11.83 ± 0.577 [8] | 11.56 ± 0.630 [8] | 0.297 |
| **%NK+CD8+** | 3.44 ± 0.173 [8] | 3.95 ± 0.235 [8] | 3.46 ± 0.249 [8] | 3.34 ± 0.129 [8] | 0.446 |
| **%MACSUBSET+** | 5.49 ± 0.069 [8] | 5.61 ± 0.287 [8] | 5.64 ± 0.317 [8] | 5.90 ± 0.316 [8] | 0.224 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **%CD45+** | 50.25 ± 0.904 [8] | 10.34 ± 1.289 [8]\*\* | <.001 |
| **%CD5+** | 30.98 ± 0.469 [8] | 61.84 ± 2.505 [8]\*\* | <.001 |
| **%CD4+CD5+** | 19.26 ± 0.748 [8] | 24.44 ± 1.618 [8]\* | 0.013 |
| **%CD8+CD5+** | 11.00 ± 0.664 [8] | 34.66 ± 2.904 [8]\*\* | <.001 |
| **%MACSUBSET+** | 5.49 ± 0.069 [8] | 9.71 ± 0.865 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **1/10 AAGM1 (iv x 1)** | **Trendc** |
| --- | --- | --- | --- |
| **%NK+CD8+** | 3.44 ± 0.173 [8] | 0.33 ± 0.103 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 20 PFDA NATURAL KILLER ACTIVITY IN FEMALE RATS  STUDY 8** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **SPLEEN WT (MG)** | 586.0 ± 22.89 [8] | 568.6 ± 26.60 [8] | 575.5 ± 36.61 [8] | 553.6 ± 13.28 [8] | 0.355 |
| **%CYTO 200 E:T RATIO** | 43.46 ± 1.766 [8] | 49.66 ± 3.177 [8] | 46.24 ± 2.734 [8] | 47.00 ± 3.185 [8] | 0.364 |
| **%CYTO 100 E:T RATIO** | 32.72 ± 1.420 [8] | 37.80 ± 2.193 [8] | 34.74 ± 2.180 [8] | 35.69 ± 2.967 [8] | 0.321 |
| **%CYTO 50 E:T RATIO** | 23.50 ± 1.075 [8] | 28.58 ± 1.160 [8] | 25.14 ± 1.214 [8] | 25.82 ± 2.154 [8] | 0.512 |
| **%CYTO 25 E:T RATIO** | 16.72 ± 0.864 [8] | 21.02 ± 1.524 [8] | 18.28 ± 1.334 [8] | 19.45 ± 1.755 [8] | 0.401 |
| **%CYTO 12.5 E:T RATIO** | 12.48 ± 0.702 [8] | 15.67 ± 0.767 [8] | 13.07 ± 1.087 [8] | 14.14 ± 1.161 [8] | 0.233 |
| **%CYTO 6.25 E:T RATIO** | 9.09 ± 0.689 [8] | 10.87 ± 0.660 [8] | 9.06 ± 0.688 [8] | 9.95 ± 0.793 [8] | 0.827 |

| **Parametera** | **Vehicle Control** | **1/10 AAGM1 (iv x 1)** | **Trendc** |
| --- | --- | --- | --- |
| **SPLEEN WT (MG)** | 586.0 ± 22.89 [8] | 518.1 ± 12.73 [8]\* | 0.016 |
| **%CYTO 200 E:T RATIO** | 43.46 ± 1.766 [8] | 4.74 ± 0.729 [8]\*\* | <.001 |
| **%CYTO 100 E:T RATIO** | 32.72 ± 1.420 [8] | 4.05 ± 0.565 [8]\*\* | <.001 |
| **%CYTO 50 E:T RATIO** | 23.50 ± 1.075 [8] | 3.92 ± 0.398 [8]\*\* | <.001 |
| **%CYTO 25 E:T RATIO** | 16.72 ± 0.864 [8] | 3.56 ± 0.438 [8]\*\* | <.001 |
| **%CYTO 12.5 E:T RATIO** | 12.48 ± 0.702 [8] | 3.70 ± 0.478 [8]\*\* | <.001 |
| **%CYTO 6.25 E:T RATIO** | 9.09 ± 0.689 [8] | 3.70 ± 0.499 [8]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01]  c: For body weight and organ weight endpoints, positive control group was compared to control using a two-sample t-test.  For other endpoints, positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 21 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 8** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 170.7 ± 3.484 [8] | 166.2 ± 3.316 [8] | 166.6 ± 2.654 [8] | 166.4 ± 2.970 [8] | 168.4 ± 3.406 [8] | 163.8 ± 2.660 [8] | 0.352 |
| **BODY WGT DAY 8 (G)** | 186.5 ± 3.469 [8] | 177.9 ± 3.739 [8] | 173.2 ± 5.409 [8] | 181.1 ± 2.417 [8] | 183.8 ± 3.975 [8] | 179.3 ± 3.923 [8] | 0.600 |
| **BODY WGT DAY 15 (G)** | 199.0 ± 4.350 [8] | 189.9 ± 3.684 [8] | 195.0 ± 4.470 [8] | 192.5 ± 2.519 [8] | 193.3 ± 3.878 [8] | 185.2 ± 5.410 [8] | 0.132 |
| **BODY WGT DAY 22 (G)** | 212.2 ± 3.636 [8] | 202.4 ± 3.435 [8] | 209.4 ± 4.919 [8] | 206.0 ± 2.434 [8] | 203.6 ± 4.692 [8] | 180.6 ± 5.937 [8]\*\* | 0.001 |
| **BODY WGT DAY 29 (G)** | 219.8 ± 3.551 [8] | 211.5 ± 3.915 [8] | 216.8 ± 3.664 [8] | 217.2 ± 3.066 [8] | 203.9 ± 6.270 [8]\* | 165.0 ± 8.049 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 15.80 ± 0.721 [8] | 11.70 ± 0.958 [8] | 6.54 ± 5.632 [8] | 14.70 ± 1.759 [8] | 15.38 ± 1.386 [8] | 15.44 ± 2.084 [8] | 0.607 |
| **DAY 15- DAY 1 (G)** | 28.25 ± 1.219 [8] | 23.75 ± 1.582 [8] | 28.34 ± 2.830 [8] | 26.16 ± 1.990 [8] | 24.84 ± 1.539 [8] | 21.40 ± 3.956 [8] | 0.077 |
| **DAY 22- DAY 1 (G)** | 41.44 ± 1.073 [8] | 36.28 ± 1.167 [8] | 42.76 ± 2.778 [8] | 39.66 ± 1.468 [8] | 35.16 ± 3.258 [8] | 16.83 ± 4.627 [8]\*\* | <.001 |
| **DAY 29- DAY 1 (G)** | 49.05 ± 1.144 [8] | 45.29 ± 1.884 [8] | 50.16 ± 2.425 [8] | 50.79 ± 1.931 [8] | 35.46 ± 4.617 [8]\* | 1.18 ± 6.642 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 170.7 ± 3.484 [8] | 163.2 ± 3.045 [8] | 0.093 |
| **BODY WGT DAY 8 (G)** | 186.5 ± 3.469 [8] | 179.0 ± 4.003 [8] | 0.172 |
| **BODY WGT DAY 15 (G)** | 199.0 ± 4.350 [8] | 191.4 ± 3.979 [8] | 0.294 |
| **BODY WGT DAY 22 (G)** | 212.2 ± 3.636 [8] | 202.8 ± 2.919 [8] | 0.083 |
| **BODY WGT DAY 29 (G)** | 219.8 ± 3.551 [8] | 198.0 ± 5.649 [8]\* | 0.009 |
| **DAY 8- DAY 1 (G)** | 15.80 ± 0.721 [8] | 15.79 ± 1.392 [8] | 0.916 |
| **DAY 15- DAY 1 (G)** | 28.25 ± 1.219 [8] | 28.26 ± 2.583 [8] | 0.529 |
| **DAY 22- DAY 1 (G)** | 41.44 ± 1.073 [8] | 39.63 ± 1.584 [8] | 0.636 |
| **DAY 29- DAY 1 (G)** | 49.05 ± 1.144 [8] | 34.80 ± 3.456 [8]\*\* | 0.003 |

| **TABLE 21 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **1/10 AAGM1 (iv x 1)** | **Trendc** |
| **BODY WGT DAY 1 (G)** | 170.7 ± 3.484 [8] | 165.5 ± 2.843 [8] | 0.270 |
| **BODY WGT DAY 8 (G)** | 186.5 ± 3.469 [8] | 184.3 ± 2.649 [8] | 0.529 |
| **BODY WGT DAY 15 (G)** | 199.0 ± 4.350 [8] | 200.7 ± 2.901 [8] | 0.713 |
| **BODY WGT DAY 22 (G)** | 212.2 ± 3.636 [8] | 213.9 ± 2.912 [8] | 0.753 |
| **BODY WGT DAY 29 (G)** | 219.8 ± 3.551 [8] | 220.7 ± 2.751 [8] | 0.834 |
| **DAY 8- DAY 1 (G)** | 15.80 ± 0.721 [8] | 18.76 ± 1.032 [8]\* | 0.021 |
| **DAY 15- DAY 1 (G)** | 28.25 ± 1.219 [8] | 35.16 ± 1.317 [8]\*\* | 0.005 |
| **DAY 22- DAY 1 (G)** | 41.44 ± 1.073 [8] | 48.35 ± 2.390 [8]\* | 0.021 |
| **DAY 29- DAY 1 (G)** | 49.05 ± 1.144 [8] | 55.19 ± 2.338 [8]\* | 0.021 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 22 PFDA BONE MARROW IN FEMALE RATS  STUDY 9** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **TOT BMW CELL#X10^6** | 64.46 ± 6.140 [8] | 59.52 ± 2.604 [8] | 56.36 ± 6.410 [8] | 60.06 ± 3.893 [8] | 0.712 |
| **CFU-E/2X10^5 CELLS** | 180.6 ± 14.49 [8] | 186.5 ± 16.14 [8] | 184.3 ± 7.365 [8] | 158.1 ± 8.987 [8] | 0.264 |
| **CFU-E/FEMUR X10^4** | 5.78 ± 0.649 [8] | 5.55 ± 0.471 [8] | 5.24 ± 0.700 [8] | 4.82 ± 0.501 [8] | 0.179 |
| **BFU-E/2X10^5 CELLS** | 20.50 ± 2.841 [8] | 17.00 ± 2.315 [8] | 19.25 ± 3.016 [8] | 17.00 ± 1.773 [8] | 0.352 |
| **BFU-E/FEMUR X10^4** | 0.65 ± 0.096 [8] | 0.51 ± 0.074 [8] | 0.49 ± 0.044 [8] | 0.45 ± 0.080 [8] | 0.114 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **TOT BMW CELL#X10^6** | 64.46 ± 6.140 [8] | 10.32 ± 1.043 [8]\*\* | <.001 |
| **CFU-E/2X10^5 CELLS** | 180.6 ± 14.49 [8] | 5.63 ± 2.367 [8]\*\* | <.001 |
| **CFU-E/FEMUR X10^4** | 5.78 ± 0.649 [8] | 0.03 ± 0.013 [8]\*\* | <.001 |
| **BFU-E/2X10^5 CELLS** | 20.50 ± 2.841 [8] | 1.00 ± 0.500 [8]\*\* | <.001 |
| **BFU-E/FEMUR X10^4** | 0.65 ± 0.096 [8] | 0.01 ± 0.003 [8]\*\* | <.001 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 23 PFDA % BONE MARROW DIFFERENTIALS IN FEMALE RATS  STUDY 9** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **%CD45RA+** | 19.01 ± 0.999 [8] | 19.64 ± 0.571 [8] | 20.83 ± 1.226 [8] | 19.20 ± 1.003 [8] | 0.699 |
| **%CD3+** | 1.93 ± 0.224 [8] | 1.86 ± 0.143 [8] | 1.91 ± 0.184 [8] | 1.91 ± 0.143 [8] | 0.636 |
| **%CD11B/C+** | 41.65 ± 1.461 [8] | 38.39 ± 1.249 [8] | 36.15 ± 1.163 [8]\* | 39.16 ± 1.129 [8] | 0.226 |
| **%CD71+** | 28.38 ± 1.127 [8] | 29.46 ± 1.016 [8] | 31.24 ± 0.853 [8] | 31.26 ± 0.612 [8] | 0.014 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **%CD45RA+** | 19.01 ± 0.999 [8] | 0.30 ± 0.065 [8]\*\* | <.001 |
| **%CD3+** | 1.93 ± 0.224 [8] | 0.33 ± 0.080 [8]\*\* | <.001 |
| **%CD11B/C+** | 41.65 ± 1.461 [8] | 1.23 ± 0.140 [8]\*\* | <.001 |
| **%CD71+** | 28.38 ± 1.127 [8] | 0.76 ± 0.224 [8]\*\* | <.001 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 24 PFDA ABSOLUTE BONE MARROW DIFFERENTIALS IN FEMALE RATS  STUDY 9** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **TOT BMW CELL#X10^6** | 64.46 ± 6.140 [8] | 59.52 ± 2.604 [8] | 56.36 ± 6.410 [8] | 60.06 ± 3.893 [8] | 0.712 |
| **ABSOL CD45RA+** | 12.44 ± 1.646 [8] | 11.67 ± 0.598 [8] | 11.86 ± 1.547 [8] | 11.65 ± 1.152 [8] | 0.880 |
| **ABSOL CD3+** | 1.25 ± 0.237 [8] | 1.11 ± 0.122 [8] | 1.14 ± 0.194 [8] | 1.13 ± 0.070 [8] | 0.893 |
| **ABSOL CD11B/C+** | 26.43 ± 2.171 [8] | 22.96 ± 1.487 [8] | 20.25 ± 2.279 [8] | 23.55 ± 1.755 [8] | 0.260 |
| **ABSOL CD71+** | 18.40 ± 1.967 [8] | 17.51 ± 0.942 [8] | 17.73 ± 2.187 [8] | 18.82 ± 1.343 [8] | 0.853 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **TOT BMW CELL#X10^6** | 64.46 ± 6.140 [8] | 10.32 ± 1.043 [8]\*\* | <.001 |
| **ABSOL CD45RA+** | 12.44 ± 1.646 [8] | 0.01 ± 0.013 [8]\*\* | <.001 |
| **ABSOL CD3+** | 1.25 ± 0.237 [8] | 0.01 ± 0.013 [8]\*\* | <.001 |
| **ABSOL CD11B/C+** | 26.43 ± 2.171 [8] | 0.15 ± 0.027 [8]\*\* | <.001 |
| **ABSOL CD71+** | 18.40 ± 1.967 [8] | 0.08 ± 0.037 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 25 PFDA DNA SYNTHESIS IN FEMALE RATS  STUDY 9** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **TOTAL CELLS (X 10^6)** | 64.46 ± 6.140 [8] | 59.52 ± 2.604 [8] | 56.36 ± 6.410 [8] | 60.06 ± 3.893 [8] | 0.712 |
| **DNA SYNTHESIS (CPM)** | 41784 ± 5122 [8] | 50905 ± 9202 [8] | 55818 ± 4634 [8] | 53523 ± 4466 [8] | 0.122 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **TOTAL CELLS (X 10^6)** | 64.46 ± 6.140 [8] | 10.32 ± 1.043 [8]\*\* | <.001 |
| **DNA SYNTHESIS (CPM)** | 41784 ± 5122 [8] | 4122 ± 344.2 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 26 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 9** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 177.8 ± 3.063 [8] | 181.7 ± 2.451 [8] | 178.9 ± 2.045 [8] | 178.2 ± 3.099 [8] | 180.4 ± 1.038 [8] | 183.8 ± 1.755 [8] | 0.162 |
| **BODY WGT DAY 8 (G)** | 190.1 ± 2.882 [8] | 196.6 ± 3.036 [8] | 192.9 ± 2.844 [8] | 194.6 ± 3.203 [8] | 193.3 ± 2.165 [8] | 196.3 ± 2.255 [8] | 0.275 |
| **BODY WGT DAY 15 (G)** | 200.4 ± 3.439 [8] | 207.3 ± 2.805 [8] | 204.2 ± 2.752 [8] | 206.9 ± 3.764 [8] | 204.0 ± 2.544 [8] | 195.9 ± 2.897 [8] | 0.244 |
| **BODY WGT DAY 22 (G)** | 211.1 ± 4.687 [8] | 219.9 ± 3.186 [8] | 218.6 ± 3.478 [8] | 220.6 ± 3.723 [8] | 213.7 ± 3.275 [8] | 190.9 ± 3.295 [8]\*\* | 0.011 |
| **BODY WGT DAY 29 (G)** | 217.0 ± 6.523 [8] | 226.2 ± 3.397 [8] | 227.1 ± 4.783 [8] | 226.8 ± 3.375 [8] | 211.6 ± 4.038 [8] | 170.6 ± 4.228 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 12.29 ± 0.850 [8] | 14.89 ± 1.541 [8] | 14.08 ± 1.638 [8] | 16.35 ± 1.570 [8] | 12.91 ± 1.932 [8] | 12.54 ± 0.952 [8] | 0.878 |
| **DAY 15- DAY 1 (G)** | 22.66 ± 1.028 [8] | 25.55 ± 1.842 [8] | 25.30 ± 1.504 [8] | 28.68 ± 2.151 [8] | 23.63 ± 2.406 [8] | 12.11 ± 2.498 [8]\*\* | 0.106 |
| **DAY 22- DAY 1 (G)** | 33.34 ± 2.446 [8] | 38.20 ± 2.412 [8] | 39.71 ± 1.921 [8] | 42.39 ± 2.457 [8] | 33.34 ± 2.926 [8] | 7.19 ± 3.147 [8]\*\* | 0.015 |
| **DAY 29- DAY 1 (G)** | 39.24 ± 4.918 [8] | 44.45 ± 3.012 [8] | 48.28 ± 3.784 [8] | 48.59 ± 1.349 [8] | 31.20 ± 3.635 [8] | -13.1 ± 4.505 [8]\*\* | 0.002 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 177.8 ± 3.063 [8] | 181.9 ± 2.534 [8] | 0.172 |
| **BODY WGT DAY 8 (G)** | 190.1 ± 2.882 [8] | 198.1 ± 3.161 [8] | 0.115 |
| **BODY WGT DAY 15 (G)** | 200.4 ± 3.439 [8] | 209.4 ± 3.124 [8] | 0.052 |
| **BODY WGT DAY 22 (G)** | 211.1 ± 4.687 [8] | 221.3 ± 3.101 [8] | 0.093 |
| **BODY WGT DAY 29 (G)** | 217.0 ± 6.523 [8] | 210.3 ± 2.518 [8] | 0.600 |
| **DAY 8- DAY 1 (G)** | 12.29 ± 0.850 [8] | 16.14 ± 1.433 [8]\* | 0.046 |
| **DAY 15- DAY 1 (G)** | 22.66 ± 1.028 [8] | 27.44 ± 1.129 [8]\*\* | 0.016 |
| **DAY 22- DAY 1 (G)** | 33.34 ± 2.446 [8] | 39.38 ± 1.212 [8]\* | 0.074 |
| **DAY 29- DAY 1 (G)** | 39.24 ± 4.918 [8] | 28.38 ± 1.586 [8] | 0.031 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 27 PFDA T DEPENDENT AB RESPONSE DAY 4 IN FEMALE RATS  STUDY 10** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **IGM PFC/10^6 SP.C.** | 582.6 ± 88.04 [8] | 566.5 ± 75.02 [8] | 688.4 ± 101.3 [8] | 520.8 ± 90.87 [8] | 0.893 |
| **IGM PFC/SPLEEN 10^3** | 608.6 ± 97.56 [8] | 517.5 ± 60.63 [8] | 670.9 ± 106.7 [8] | 452.6 ± 68.53 [8] | 0.626 |
| **CELLS/SPLEEN 10^7** | 105.3 ± 5.603 [8] | 92.85 ± 3.583 [8] | 97.10 ± 3.210 [8] | 89.97 ± 4.199 [8]\* | 0.039 |
| **SPLEEN WEIGHT (MG)** | 638.8 ± 26.42 [8] | 580.0 ± 14.02 [8] | 610.0 ± 11.34 [8] | 588.8 ± 24.45 [8] | 0.200 |
| **BODY WEIGHT (G)** | 217.8 ± 7.815 [8] | 209.9 ± 3.381 [8] | 219.4 ± 3.834 [8] | 212.0 ± 4.670 [8] | 0.867 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **IGM PFC/10^6 SP.C.** | 582.6 ± 88.04 [8] | 2.95 ± 0.773 [8]\*\* | <.001 |
| **IGM PFC/SPLEEN 10^3** | 608.6 ± 97.56 [8] | 1.00 ± 0.000 [8]\*\* | <.001 |
| **CELLS/SPLEEN 10^7** | 105.3 ± 5.603 [8] | 14.99 ± 1.465 [8]\*\* | <.001 |
| **SPLEEN WEIGHT (MG)** | 638.8 ± 26.42 [8] | 255.0 ± 16.58 [8]\*\* | <.001 |
| **BODY WEIGHT (G)** | 217.8 ± 7.815 [8] | 198.1 ± 3.602 [8]\* | 0.046 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: For body weight and organ weight endpoints, each dose was compared to the control with Dunnett’s test when a trend was present (P<.01 from Jonckheere’s trend test),  or with Williams’ test when no trend was present.  For other endpoints, each dose was compared to the control with Shirley’s test when a trend was present or with Dunns test when no trend was present.  [\* = P<0.05, \*\* = P<0.01]  c: For body weight and organ weight endpoints, positive control group was compared to control using a two-sample t-test.  For other endpoints, positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 28 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 10** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 156.5 ± 1.808 [8] | 153.5 ± 1.749 [8] | 156.4 ± 2.268 [8] | 152.8 ± 2.466 [8] | 155.8 ± 2.200 [8] | 161.9 ± 4.123 [8] | 0.286 |
| **BODY WGT DAY 8 (G)** | 175.2 ± 4.058 [8] | 170.1 ± 2.414 [8] | 175.7 ± 2.770 [8] | 172.0 ± 2.713 [8] | 175.6 ± 2.585 [8] | 181.6 ± 4.698 [8] | 0.283 |
| **BODY WGT DAY 15 (G)** | 191.0 ± 5.628 [8] | 185.8 ± 2.897 [8] | 190.9 ± 3.125 [8] | 187.4 ± 3.503 [8] | 192.8 ± 3.478 [8] | 192.8 ± 5.090 [8] | 0.459 |
| **BODY WGT DAY 22 (G)** | 205.4 ± 6.807 [8] | 201.1 ± 3.414 [8] | 206.7 ± 3.457 [8] | 200.1 ± 3.935 [8] | 203.5 ± 3.344 [8] | 189.0 ± 7.606 [8] | 0.100 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 7.815 [8] | 209.9 ± 3.381 [8] | 219.4 ± 3.834 [8] | 212.0 ± 4.670 [8] | 212.8 ± 5.048 [8] | 178.4 ± 7.034 [8]\*\* | 0.016 |
| **DAY 8- DAY 1 (G)** | 18.71 ± 2.367 [8] | 16.51 ± 1.282 [8] | 19.24 ± 1.945 [8] | 19.20 ± 0.916 [8] | 19.82 ± 1.312 [8] | 19.73 ± 2.207 [8] | 0.146 |
| **DAY 15- DAY 1 (G)** | 34.46 ± 3.894 [8] | 32.30 ± 1.758 [8] | 34.45 ± 1.817 [8] | 34.61 ± 1.391 [8] | 37.01 ± 2.275 [8] | 30.90 ± 2.543 [8] | 0.481 |
| **DAY 22- DAY 1 (G)** | 48.86 ± 5.175 [8] | 47.56 ± 2.574 [8] | 50.26 ± 2.256 [8] | 47.31 ± 1.668 [8] | 47.74 ± 2.475 [8] | 27.16 ± 5.534 [8]\*\* | 0.027 |
| **DAY 29- DAY 1 (G)** | 61.24 ± 6.287 [8] | 56.33 ± 2.466 [8] | 62.95 ± 2.674 [8] | 59.21 ± 2.750 [8] | 57.06 ± 3.967 [8] | 16.50 ± 4.603 [8]\*\* | 0.003 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 156.5 ± 1.808 [8] | 152.5 ± 2.285 [8] | 0.103 |
| **BODY WGT DAY 8 (G)** | 175.2 ± 4.058 [8] | 175.5 ± 2.905 [8] | 0.916 |
| **BODY WGT DAY 15 (G)** | 191.0 ± 5.628 [8] | 192.5 ± 4.209 [8] | 0.916 |
| **BODY WGT DAY 22 (G)** | 205.4 ± 6.807 [8] | 205.5 ± 4.640 [8] | 0.916 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 7.815 [8] | 198.1 ± 3.602 [8]\* | 0.046 |
| **DAY 8- DAY 1 (G)** | 18.71 ± 2.367 [8] | 23.00 ± 2.013 [8] | 0.156 |
| **DAY 15- DAY 1 (G)** | 34.46 ± 3.894 [8] | 39.98 ± 3.942 [8] | 0.600 |
| **DAY 22- DAY 1 (G)** | 48.86 ± 5.175 [8] | 53.03 ± 4.061 [8] | 0.462 |
| **DAY 29- DAY 1 (G)** | 61.24 ± 6.287 [8] | 45.61 ± 2.998 [8]\* | 0.093 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 29 PFDA HEMATOLOGY IN FEMALE RATS  STUDY 11** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **LEUKOCYTE (10^3/UL)** | 11.40 ± 0.313 [8] | 14.15 ± 1.416 [8] | 12.11 ± 1.072 [8] | 10.83 ± 1.300 [8] | 0.933 |
| **ERYTHROCYTE (10^6/UL)** | 6.58 ± 0.079 [8] | 6.87 ± 0.135 [8] | 7.09 ± 0.223 [8] | 6.63 ± 0.134 [8] | 0.762 |
| **HEMOGLOBIN (G/DL)** | 14.21 ± 0.126 [8] | 14.40 ± 0.254 [8] | 14.14 ± 0.217 [8] | 13.68 ± 0.233 [8] | 0.059 |
| **HEMATOCRIT (%)** | 36.40 ± 0.461 [8] | 37.90 ± 0.441 [8] | 38.79 ± 1.177 [8] | 36.64 ± 0.579 [8] | 0.711 |
| **MCV (FL)** | 55.33 ± 0.427 [8] | 55.21 ± 0.655 [8] | 54.73 ± 0.660 [8] | 55.33 ± 0.392 [8] | 0.920 |
| **MCH (PG)** | 21.64 ± 0.336 [8] | 20.96 ± 0.283 [8] | 20.01 ± 0.375 [8]\*\* | 20.65 ± 0.204 [8] | 0.016 |
| **MCHC (G/DL)** | 39.10 ± 0.638 [8] | 37.98 ± 0.307 [8] | 36.58 ± 0.692 [8]\* | 37.33 ± 0.381 [8]\* | 0.009 |
| **PLATELET (10^3/UL)** | 1232 ± 98.98 [8] | 984.8 ± 131.9 [8] | 1084 ± 99.48 [8] | 1114 ± 77.90 [8] | 0.814 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **LEUKOCYTE (10^3/UL)** | 11.40 ± 0.313 [8] | 2.08 ± 0.448 [8]\*\* | <.001 |
| **ERYTHROCYTE (10^6/UL)** | 6.58 ± 0.079 [8] | 6.52 ± 0.180 [8] | 0.401 |
| **HEMOGLOBIN (G/DL)** | 14.21 ± 0.126 [8] | 13.60 ± 0.325 [8] | 0.155 |
| **HEMATOCRIT (%)** | 36.40 ± 0.461 [8] | 36.03 ± 1.030 [8] | 0.563 |
| **MCV (FL)** | 55.33 ± 0.427 [8] | 55.24 ± 0.577 [8] | 0.875 |
| **MCH (PG)** | 21.64 ± 0.336 [8] | 20.89 ± 0.324 [8] | 0.207 |
| **MCHC (G/DL)** | 39.10 ± 0.638 [8] | 37.79 ± 0.409 [8] | 0.103 |
| **PLATELET (10^3/UL)** | 1232 ± 98.98 [8] | 458.6 ± 60.21 [8]\*\* | <.001 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 30 PFDA ABSOLUTE LEUKOCYTE DIFFERENTIALS IN FEMALE RATS  STUDY 11** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **LEUKOCYTES (10^3/MM^3)** | 11.40 ± 0.313 [8] | 14.15 ± 1.416 [8] | 12.11 ± 1.072 [8] | 10.83 ± 1.300 [8] | 0.933 |
| **% LYMPHOCYTES** | 60.45 ± 0.978 [8] | 62.31 ± 1.739 [8] | 58.30 ± 1.867 [8] | 59.05 ± 2.696 [8] | 0.168 |
| **% NEUTROPHILS** | 33.94 ± 0.877 [8] | 31.74 ± 1.427 [8] | 35.76 ± 1.795 [8] | 34.88 ± 2.134 [8] | 0.214 |
| **% MONOCYTES** | 3.99 ± 0.405 [8] | 3.91 ± 0.454 [8] | 4.10 ± 0.342 [8] | 4.30 ± 0.622 [8] | 0.674 |
| **% EOSINOPHILS** | 1.39 ± 0.314 [8] | 1.61 ± 0.266 [8] | 1.47 ± 0.360 [8] | 1.33 ± 0.256 [8] | 0.650 |
| **%BASOPHILS** | 0.23 ± 0.125 [8] | 0.43 ± 0.194 [8] | 0.36 ± 0.157 [8] | 0.43 ± 0.157 [8] | 0.814 |
| **ABS LYMPHOCYTES** | 6.90 ± 0.253 [8] | 8.72 ± 0.745 [8] | 6.99 ± 0.544 [8] | 6.34 ± 0.761 [8] | 0.687 |
| **ABS NEUTROPHILS** | 3.86 ± 0.075 [8] | 4.53 ± 0.531 [8] | 4.38 ± 0.468 [8] | 3.80 ± 0.508 [8] | 0.946 |
| **ABS MONOCYTES** | 0.46 ± 0.052 [8] | 0.58 ± 0.115 [8] | 0.50 ± 0.063 [8] | 0.47 ± 0.103 [8] | 0.590 |
| **ABS EOSINOPHILS** | 0.16 ± 0.038 [8] | 0.25 ± 0.064 [8] | 0.20 ± 0.060 [8] | 0.16 ± 0.044 [8] | 0.686 |
| **ABS BASOPHILS** | 0.03 ± 0.017 [8] | 0.07 ± 0.042 [8] | 0.05 ± 0.024 [8] | 0.06 ± 0.023 [8] | 0.635 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 30 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| **LEUKOCYTES (10^3/MM^3)** | 11.40 ± 0.313 [8] | 2.08 ± 0.448 [8]\*\* | <.001 |
| **% LYMPHOCYTES** | 60.45 ± 0.978 [8] | 44.08 ± 2.672 [8]\*\* | <.001 |
| **% NEUTROPHILS** | 33.94 ± 0.877 [8] | 42.20 ± 2.865 [8]\*\* | 0.005 |
| **% MONOCYTES** | 3.99 ± 0.405 [8] | 8.30 ± 1.385 [8]\* | 0.012 |
| **% EOSINOPHILS** | 1.39 ± 0.314 [8] | 3.90 ± 1.001 [8]\* | 0.046 |
| **%BASOPHILS** | 0.23 ± 0.125 [8] | 1.54 ± 0.632 [8]\* | 0.046 |
| **ABS LYMPHOCYTES** | 6.90 ± 0.253 [8] | 0.93 ± 0.223 [8]\*\* | <.001 |
| **ABS NEUTROPHILS** | 3.86 ± 0.075 [8] | 0.84 ± 0.146 [8]\*\* | <.001 |
| **ABS MONOCYTES** | 0.46 ± 0.052 [8] | 0.15 ± 0.032 [8]\*\* | 0.002 |
| **ABS EOSINOPHILS** | 0.16 ± 0.038 [8] | 0.11 ± 0.046 [8] | 0.399 |
| **ABS BASOPHILS** | 0.03 ± 0.017 [8] | 0.05 ± 0.023 [8] | 0.779 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 31 PFDA RETICULOCYTES IN FEMALE RATS  STUDY 11** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **RETICS (%)** | 3.18 ± 0.096 [8] | 3.44 ± 0.224 [8] | 2.91 ± 0.128 [8] | 2.98 ± 0.096 [8] | 0.103 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **RETICS (%)** | 3.18 ± 0.096 [8] | 0.05 ± 0.009 [8]\*\* | <.001 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Shirley’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunn’s test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using rank sum test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 32 PFDA ORGAN WEIGHTS IN FEMALE RATS  STUDY 11** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **Trendb** |
| **BODY WGT (G)** | 217.8 ± 5.789 [8] | 217.0 ± 4.233 [8] | 212.2 ± 4.887 [8] | 211.5 ± 5.082 [8] | 0.184 |
| **LIVER (MG)** | 8766 ± 336.5 [8] | 8831 ± 363.6 [8] | 9215 ± 228.9 [8] | 9906 ± 389.4 [8] | 0.030 |
| **SPLEEN (MG)** | 591.3 ± 19.32 [8] | 624.9 ± 31.20 [8] | 604.9 ± 29.47 [8] | 539.0 ± 33.46 [8] | 0.267 |
| **LUNGS (MG)** | 1447 ± 72.60 [8] | 1539 ± 88.85 [8] | 1541 ± 87.50 [8] | 1517 ± 55.15 [8] | 0.556 |
| **THYMUS (MG)** | 312.9 ± 10.72 [8] | 297.4 ± 16.59 [8] | 320.9 ± 23.26 [8] | 308.8 ± 23.36 [8] | 0.814 |
| **KIDNEY (MG)** | 1618 ± 42.71 [8] | 1722 ± 38.12 [8] | 1723 ± 32.24 [8] | 1791 ± 63.93 [8]\* | 0.006 |
| **ADRENALS (MG)** | 107.5 ± 7.008 [8] | 106.6 ± 4.996 [8] | 109.0 ± 7.407 [8] | 96.38 ± 4.873 [8] | 0.267 |
| **LIVER /BODY (%)** | 4.02 ± 0.102 [8] | 4.06 ± 0.097 [8] | 4.35 ± 0.102 [8]\* | 4.68 ± 0.121 [8]\*\* | <.001 |
| **SPLEEN /BODY (%)** | 0.27 ± 0.013 [8] | 0.29 ± 0.010 [8] | 0.28 ± 0.012 [8] | 0.25 ± 0.013 [8] | 0.236 |
| **LUNGS /BODY (%)** | 0.66 ± 0.028 [8] | 0.71 ± 0.038 [8] | 0.73 ± 0.036 [8] | 0.72 ± 0.027 [8] | 0.259 |
| **THYMUS /BODY (%)** | 0.15 ± 0.006 [8] | 0.14 ± 0.008 [8] | 0.15 ± 0.009 [8] | 0.15 ± 0.009 [8] | 0.671 |
| **KIDNEY /BODY (%)** | 0.75 ± 0.016 [8] | 0.80 ± 0.020 [8] | 0.82 ± 0.017 [8]\* | 0.85 ± 0.023 [8]\*\* | 0.001 |
| **ADRENAL/BODY (%)** | 0.05 ± 0.003 [8] | 0.05 ± 0.003 [8] | 0.05 ± 0.004 [8] | 0.05 ± 0.003 [8] | 0.294 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 32 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| **BODY WGT (G)** | 217.8 ± 5.789 [8] | 197.7 ± 4.010 [8]\* | 0.027 |
| **LIVER (MG)** | 8766 ± 336.5 [8] | 7198 ± 177.9 [8]\*\* | 0.002 |
| **SPLEEN (MG)** | 591.3 ± 19.32 [8] | 267.4 ± 12.69 [8]\*\* | <.001 |
| **LUNGS (MG)** | 1447 ± 72.60 [8] | 1748 ± 116.1 [8]\* | 0.172 |
| **THYMUS (MG)** | 312.9 ± 10.72 [8] | 100.5 ± 9.266 [8]\*\* | <.001 |
| **KIDNEY (MG)** | 1618 ± 42.71 [8] | 1544 ± 28.77 [8] | 0.208 |
| **ADRENALS (MG)** | 107.5 ± 7.008 [8] | 82.63 ± 6.910 [8]\* | 0.035 |
| **LIVER /BODY (%)** | 4.02 ± 0.102 [8] | 3.64 ± 0.075 [8]\*\* | 0.012 |
| **SPLEEN /BODY (%)** | 0.27 ± 0.013 [8] | 0.14 ± 0.006 [8]\*\* | <.001 |
| **LUNGS /BODY (%)** | 0.66 ± 0.028 [8] | 0.88 ± 0.057 [8]\*\* | 0.003 |
| **THYMUS /BODY (%)** | 0.15 ± 0.006 [8] | 0.05 ± 0.005 [8]\*\* | <.001 |
| **KIDNEY /BODY (%)** | 0.75 ± 0.016 [8] | 0.78 ± 0.015 [8] | 0.187 |
| **ADRENAL/BODY (%)** | 0.05 ± 0.003 [8] | 0.04 ± 0.003 [8]\* | 0.042 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

| **TABLE 33 PFDA BODY WEIGHTS IN FEMALE RATS  STUDY 11** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.125 mg/kg** | **0.25 mg/kg** | **0.5 mg/kg** | **1.0 mg/kg** | **2.0 mg/kg** | **Trendb** |
| **BODY WGT DAY 1 (G)** | 175.3 ± 4.697 [8] | 173.1 ± 3.143 [8] | 173.1 ± 4.471 [8] | 170.7 ± 3.560 [8] | 171.9 ± 3.878 [8] | 169.2 ± 2.823 [8] | 0.240 |
| **BODY WGT DAY 8 (G)** | 188.0 ± 4.532 [8] | 190.4 ± 3.351 [8] | 188.1 ± 4.547 [8] | 185.2 ± 4.736 [8] | 187.6 ± 1.761 [8] | 185.6 ± 2.680 [8] | 0.367 |
| **BODY WGT DAY 15 (G)** | 196.3 ± 4.689 [8] | 197.0 ± 4.266 [8] | 195.1 ± 4.242 [8] | 193.5 ± 4.246 [8] | 195.0 ± 2.432 [8] | 190.0 ± 1.929 [8] | 0.156 |
| **BODY WGT DAY 22 (G)** | 206.7 ± 4.624 [8] | 208.2 ± 4.715 [8] | 204.3 ± 4.732 [8] | 203.3 ± 3.989 [8] | 207.3 ± 3.001 [8] | 184.7 ± 2.980 [8]\*\* | 0.007 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 5.789 [8] | 217.0 ± 4.233 [8] | 212.2 ± 4.887 [8] | 211.5 ± 5.082 [8] | 211.2 ± 3.100 [8] | 180.6 ± 5.167 [8]\*\* | <.001 |
| **DAY 8- DAY 1 (G)** | 12.74 ± 2.793 [8] | 17.33 ± 2.670 [8] | 15.04 ± 2.221 [8] | 14.51 ± 2.675 [8] | 15.65 ± 3.151 [8] | 16.38 ± 1.019 [8] | 0.569 |
| **DAY 15- DAY 1 (G)** | 21.08 ± 2.823 [8] | 23.96 ± 2.198 [8] | 22.03 ± 1.230 [8] | 22.75 ± 2.866 [8] | 23.13 ± 3.188 [8] | 20.79 ± 2.690 [8] | 0.978 |
| **DAY 22- DAY 1 (G)** | 31.40 ± 2.877 [8] | 35.13 ± 2.597 [8] | 31.24 ± 2.313 [8] | 32.54 ± 3.429 [8] | 35.41 ± 3.204 [8] | 15.45 ± 3.558 [8]\*\* | 0.053 |
| **DAY 29- DAY 1 (G)** | 42.56 ± 3.532 [8] | 43.94 ± 2.513 [8] | 39.13 ± 2.723 [8] | 40.74 ± 3.978 [8] | 39.28 ± 2.946 [8] | 11.38 ± 5.557 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **50 mg/kg CPS (ip x 4)** | **Trendc** |
| --- | --- | --- | --- |
| **BODY WGT DAY 1 (G)** | 175.3 ± 4.697 [8] | 168.8 ± 3.218 [8] | 0.294 |
| **BODY WGT DAY 8 (G)** | 188.0 ± 4.532 [8] | 186.0 ± 3.241 [8] | 0.599 |
| **BODY WGT DAY 15 (G)** | 196.3 ± 4.689 [8] | 195.6 ± 3.745 [8] | 0.834 |
| **BODY WGT DAY 22 (G)** | 206.7 ± 4.624 [8] | 208.3 ± 3.526 [8] | 0.958 |
| **BODY WGT DAY 29 (G)** | 217.8 ± 5.789 [8] | 197.7 ± 4.010 [8]\* | 0.027 |
| **DAY 8- DAY 1 (G)** | 12.74 ± 2.793 [8] | 17.24 ± 2.353 [8] | 0.208 |
| **DAY 15- DAY 1 (G)** | 21.08 ± 2.823 [8] | 26.81 ± 2.093 [8] | 0.074 |
| **DAY 22- DAY 1 (G)** | 31.40 ± 2.877 [8] | 39.53 ± 2.464 [8]\* | 0.016 |
| **DAY 29- DAY 1 (G)** | 42.56 ± 3.532 [8] | 28.91 ± 3.850 [8]\* | 0.021 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Dunnett’s test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Williams’ test was applied.  [\* = P<0.05, \*\* = P<0.01]  c: Positive control group was compared to control using a two-sample t-test. Trend p-value was calculated using Jonckheere’s test. |

**APPENDIX A**

**EXTREME VALUES**

No outliers were removed.

**APPENDIX B**

**STATISTICAL METHODS**

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Hematology, hormone data, and other non-weight endpoints, which typically have skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response (Dunnett's or Dunn's test). Trend-sensitive tests were used when Jonckheere's test was significant at p<0.01.

Comparisons involving just the vehicle and positive control were performed using a t-test for organ and body weights and a rank sum test for all other endpoints.

Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel. Implausible values, extreme values from animals that were suspected of being sick due to causes other than treatment, and values that the laboratory indicated as being inadequate due to measurement problems were eliminated from the analysis. A list of these values is provided in Appendix A.

**APPENDIX C**

**REFERENCES**

Dixon, W. and Massey, F. (1951). Introduction to Statistical Analysis. McGraw Hill, New York, pp. 145-147.

Dunn, O.J. (1964). Multiple comparisons using rank sums. Technometrics 6: 241-252.

Dunnett, W. (1955). A multiple comparison procedure for comparing several treatments with a control. JASA 50: 1095-1121.

Jonckheere, A.R. (1954). A distribution-free k-sample test against ordered alternatives. Biometrika 41: 133-145.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. Biometrics 33: 386-389.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. Biometrics 27: 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. Biometrics 28: 519-531.

Williams, D.A. (1986). A note on Shirley's nonparametric test for comparing several dose levels with a zero-dose control. Biometrics 42: 183-186.