**STATISTICAL ANALYSIS**

**IMMUNOTOX STUDY**

**OF**

**PERFLUORODECANOIC ACID**

**IN FEMALE MICE**

**PREPARED FOR**

**National Institute of Environmental Health Sciences**

**National Toxicology Program**

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**September 26, 2016**

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| **TABLE 1 PFDA ORGAN WT IN FEMALE MICE  STUDY 1** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Liver mg** | 1122.0 ± 30.61 [8] | 1198.4 ± 44.52 [8] | 1415.3 ± 53.87 [8]\*\* | 1418.9 ± 59.44 [8]\*\* | 1768.4 ± 59.70 [8]\*\* | 2117.3 ± 74.75 [8]\*\* | <.001 |
| **Spleen mg** | 75.00 ± 2.471 [8] | 72.63 ± 2.853 [8] | 77.13 ± 3.627 [8] | 61.75 ± 3.081 [8] | 70.50 ± 2.639 [8] | 60.38 ± 3.525 [8]\*\* | 0.003 |
| **Lung mg** | 212.75 ± 11.34 [8] | 227.13 ± 6.275 [8] | 220.50 ± 8.834 [8] | 197.13 ± 7.724 [8] | 203.38 ± 10.10 [8] | 204.25 ± 10.26 [8] | 0.178 |
| **Thymus mg** | 59.13 ± 5.002 [8] | 63.50 ± 4.149 [8] | 70.13 ± 5.668 [8] | 62.25 ± 2.877 [8] | 65.00 ± 3.495 [8] | 59.25 ± 3.150 [8] | 0.551 |
| **Kidney mg** | 346.50 ± 13.30 [8] | 349.00 ± 15.34 [8] | 378.75 ± 7.035 [8] | 349.25 ± 13.65 [8] | 343.00 ± 10.15 [8] | 335.88 ± 13.22 [8] | 0.263 |
| **Liver/ body %** | 4.83 ± 0.082 [8] | 5.01 ± 0.105 [8] | 5.61 ± 0.066 [8]\*\* | 6.14 ± 0.113 [8]\*\* | 7.31 ± 0.100 [8]\*\* | 8.76 ± 0.176 [8]\*\* | <.001 |
| **Spleen/ body %** | 0.32 ± 0.008 [8] | 0.31 ± 0.010 [8] | 0.30 ± 0.008 [8] | 0.27 ± 0.011 [8]\*\* | 0.29 ± 0.010 [8]\*\* | 0.25 ± 0.012 [8]\*\* | <.001 |
| **Lung/ body %** | 0.92 ± 0.054 [8] | 0.95 ± 0.034 [8] | 0.88 ± 0.050 [8] | 0.85 ± 0.020 [8] | 0.84 ± 0.032 [8] | 0.85 ± 0.046 [8] | 0.206 |
| **Thymus/ body %** | 0.26 ± 0.024 [8] | 0.27 ± 0.014 [8] | 0.28 ± 0.020 [8] | 0.27 ± 0.012 [8] | 0.27 ± 0.017 [8] | 0.25 ± 0.016 [8] | 0.486 |
| **Kidney/ body %** | 1.49 ± 0.048 [8] | 1.46 ± 0.041 [8] | 1.51 ± 0.050 [8] | 1.52 ± 0.045 [8] | 1.42 ± 0.022 [8] | 1.39 ± 0.042 [8] | 0.069 |

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

| **TABLE 1 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| **Liver mg** | 1122.0 ± 30.61 [8] | 1087.1 ± 57.49 [8] | 0.834 |
| **Spleen mg** | 75.00 ± 2.471 [8] | 41.88 ± 3.314 [8]\*\* | <.001 |
| **Lung mg** | 212.75 ± 11.34 [8] | 223.88 ± 9.029 [8] | 0.294 |
| **Thymus mg** | 59.13 ± 5.002 [8] | 29.75 ± 3.594 [8]\*\* | 0.002 |
| **Kidney mg** | 346.50 ± 13.30 [8] | 348.13 ± 16.45 [8] | 0.916 |
| **Liver/ body %** | 4.83 ± 0.082 [8] | 4.56 ± 0.147 [8] | 0.093 |
| **Spleen/ body %** | 0.32 ± 0.008 [8] | 0.17 ± 0.011 [8]\*\* | <.001 |
| **Lung/ body %** | 0.92 ± 0.054 [8] | 0.95 ± 0.075 [8] | 0.833 |
| **Thymus/ body %** | 0.26 ± 0.024 [8] | 0.12 ± 0.013 [8]\*\* | <.001 |
| **Kidney/ body %** | 1.49 ± 0.048 [8] | 1.46 ± 0.041 [8] | 0.833 |

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| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 2 PFDA HEMATOLOGY IN FEMALE MICE  STUDY 1** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Leukocyte (10^3/ul)** | 7.72 ± 1.065 [8] | 7.47 ± 0.912 [8] | 6.52 ± 0.848 [8] | 6.21 ± 0.585 [8] | 7.04 ± 0.593 [8] | 7.08 ± 0.484 [8] | 0.516 |
| **Erythrocyte (10^6/ul)** | 9.28 ± 0.180 [8] | 9.07 ± 0.295 [8] | 8.92 ± 0.203 [8] | 9.06 ± 0.163 [8] | 9.07 ± 0.080 [8] | 9.30 ± 0.052 [8] | 0.563 |
| **Hemoglobin (g/dl)** | 13.58 ± 0.255 [8] | 13.16 ± 0.567 [8] | 13.59 ± 0.299 [8] | 13.13 ± 0.206 [8] | 13.45 ± 0.247 [8] | 13.55 ± 0.224 [8] | 0.863 |
| **Hematocrit (%)** | 44.99 ± 1.016 [8] | 44.68 ± 1.412 [8] | 44.89 ± 1.028 [8] | 45.15 ± 0.814 [8] | 44.79 ± 0.409 [8] | 45.40 ± 0.320 [8] | 0.759 |
| **MCV** | 49.14 ± 0.551 [8] | 49.31 ± 0.261 [8] | 50.33 ± 0.212 [8] | 49.83 ± 0.182 [8] | 49.38 ± 0.267 [8] | 48.84 ± 0.157 [8] | 0.066 |
| **MCH** | 14.83 ± 0.172 [8] | 14.48 ± 0.195 [8] | 15.25 ± 0.140 [8] | 14.48 ± 0.184 [8] | 14.83 ± 0.288 [8] | 14.58 ± 0.230 [8] | 0.711 |
| **MCHC** | 30.23 ± 0.564 [8] | 29.39 ± 0.466 [8] | 30.30 ± 0.323 [8] | 29.09 ± 0.342 [8] | 30.06 ± 0.612 [8] | 29.85 ± 0.502 [8] | 0.971 |
| **Platelet (10^3/ul)** | 528.50 ± 79.46 [8] | 586.25 ± 57.71 [8] | 646.63 ± 53.71 [8] | 783.25 ± 61.15 [8] | 666.38 ± 66.05 [8] | 463.63 ± 52.18 [8] | 0.942 |
| **Neutrophils %** | 21.76 ± 2.059 [8] | 23.93 ± 1.735 [8] | 25.22 ± 1.002 [8] | 20.14 ± 1.238 [8] | 25.62 ± 0.790 [8] | 25.01 ± 1.081 [8] | 0.170 |
| **Lymphocytes %** | 70.19 ± 2.159 [8] | 66.90 ± 2.565 [8] | 63.53 ± 1.256 [8] | 69.88 ± 2.825 [8] | 63.06 ± 1.433 [8] | 68.34 ± 1.753 [8] | 0.396 |
| **Monocytes %** | 4.68 ± 0.289 [8] | 5.33 ± 0.334 [8] | 5.52 ± 0.501 [8] | 4.91 ± 0.519 [8] | 4.99 ± 0.422 [8] | 4.31 ± 0.424 [8] | 0.371 |
| **Eosinophils %** | 2.46 ± 0.574 [8] | 2.75 ± 0.605 [8] | 4.06 ± 0.592 [8] | 3.43 ± 0.898 [8] | 4.56 ± 0.633 [8] | 1.68 ± 0.310 [8] | 0.843 |
| **Basophils %** | 0.91 ± 0.221 [8] | 1.08 ± 0.251 [8] | 1.66 ± 0.271 [8] | 1.65 ± 0.449 [8] | 1.77 ± 0.252 [8] | 0.65 ± 0.128 [8] | 0.971 |
| **Neutrophils abs** | 1.76 ± 0.331 [8] | 1.86 ± 0.309 [8] | 1.64 ± 0.226 [8] | 1.26 ± 0.150 [8] | 1.82 ± 0.188 [8] | 1.80 ± 0.191 [8] | 0.957 |
| **Lymphocytes abs** | 5.30 ± 0.640 [8] | 4.88 ± 0.508 [8] | 4.12 ± 0.521 [8] | 4.30 ± 0.408 [8] | 4.41 ± 0.347 [8] | 4.80 ± 0.246 [8] | 0.396 |
| **Monocytes abs** | 0.37 ± 0.064 [8] | 0.40 ± 0.063 [8] | 0.35 ± 0.051 [8] | 0.30 ± 0.040 [8] | 0.34 ± 0.030 [8] | 0.31 ± 0.042 [8] | 0.329 |
| **Eosinophils abs** | 0.22 ± 0.058 [8] | 0.24 ± 0.064 [8] | 0.29 ± 0.063 [8] | 0.25 ± 0.055 [8] | 0.34 ± 0.065 [8] | 0.13 ± 0.030 [8] | 0.545 |
| **Basophils abs** | 0.08 ± 0.022 [8] | 0.09 ± 0.028 [8] | 0.12 ± 0.027 [8] | 0.11 ± 0.031 [8] | 0.13 ± 0.025 [8] | 0.05 ± 0.011 [8] | 0.581 |
| **Reticulocytes %** | 4.50 ± 0.183 [8] | 3.95 ± 0.179 [8] | 4.02 ± 0.237 [8] | 4.06 ± 0.182 [8] | 4.10 ± 0.174 [8] | 4.23 ± 0.163 [8] | 0.738 |

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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 2 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| **Leukocyte (10^3/ul)** | 7.72 ± 1.065 [8] | 3.93 ± 0.201 [8]\* | 0.016 |
| **Erythrocyte (10^6/ul)** | 9.28 ± 0.180 [8] | 8.12 ± 0.088 [8]\*\* | 0.002 |
| **Hemoglobin (g/dl)** | 13.58 ± 0.255 [8] | 11.65 ± 0.130 [8]\*\* | <.001 |
| **Hematocrit (%)** | 44.99 ± 1.016 [8] | 40.61 ± 0.510 [8]\*\* | 0.005 |
| **MCV** | 49.14 ± 0.551 [8] | 50.04 ± 0.187 [8] | 0.171 |
| **MCH** | 14.83 ± 0.172 [8] | 14.35 ± 0.216 [8] | 0.263 |
| **MCHC** | 30.23 ± 0.564 [8] | 28.70 ± 0.407 [8] | 0.066 |
| **Platelet (10^3/ul)** | 528.50 ± 79.46 [8] | 865.25 ± 80.52 [8]\* | 0.016 |
| **Neutrophils %** | 21.76 ± 2.059 [8] | 21.22 ± 1.994 [8] | 0.916 |
| **Lymphocytes %** | 70.19 ± 2.159 [8] | 61.77 ± 3.267 [8]\* | 0.036 |
| **Monocytes %** | 4.68 ± 0.289 [8] | 6.33 ± 0.585 [8]\* | 0.046 |
| **Eosinophils %** | 2.46 ± 0.574 [8] | 7.33 ± 0.970 [8]\*\* | 0.005 |
| **Basophils %** | 0.91 ± 0.221 [8] | 3.36 ± 0.532 [8]\*\* | 0.006 |
| **Neutrophils abs** | 1.76 ± 0.331 [8] | 0.85 ± 0.108 [8]\* | 0.035 |
| **Lymphocytes abs** | 5.30 ± 0.640 [8] | 2.40 ± 0.135 [8]\*\* | 0.002 |
| **Monocytes abs** | 0.37 ± 0.064 [8] | 0.25 ± 0.027 [8] | 0.247 |
| **Eosinophils abs** | 0.22 ± 0.058 [8] | 0.29 ± 0.041 [8] | 0.430 |
| **Basophils abs** | 0.08 ± 0.022 [8] | 0.13 ± 0.023 [8] | 0.171 |
| **Reticulocytes %** | 4.50 ± 0.183 [8] | 1.30 ± 0.155 [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 3 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 1** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 21.15 ± 0.429 [8] | 22.18 ± 0.435 [8] | 22.60 ± 0.635 [8] | 21.05 ± 0.662 [8] | 21.59 ± 0.532 [8] | 21.84 ± 0.387 [8] | 0.793 |
| **Body Weight Day 8 g** | 21.76 ± 0.397 [8] | 22.39 ± 0.545 [8] | 23.24 ± 0.712 [8] | 21.43 ± 0.405 [8] | 22.07 ± 0.597 [8] | 22.36 ± 0.276 [8] | 0.773 |
| **Body Weight Day 15 g** | 21.82 ± 0.394 [8] | 23.28 ± 0.585 [8] | 24.05 ± 0.744 [8]\* | 21.95 ± 0.630 [8] | 23.16 ± 0.614 [8] | 22.94 ± 0.448 [8] | 0.303 |
| **Body Weight Day 22 g** | 22.27 ± 0.398 [8] | 23.31 ± 0.664 [8] | 24.12 ± 0.715 [8] | 22.18 ± 0.579 [8] | 23.60 ± 0.545 [8] | 23.25 ± 0.369 [8] | 0.295 |
| **Body Weight Day 29 g** | 23.23 ± 0.487 [8] | 23.89 ± 0.661 [8] | 25.24 ± 0.890 [8] | 23.09 ± 0.678 [8] | 24.21 ± 0.788 [8] | 24.16 ± 0.586 [8] | 0.487 |
| **BW Day 8-1 g** | 0.60 ± 0.198 [8] | 0.21 ± 0.219 [8] | 0.61 ± 0.668 [8] | 0.39 ± 0.360 [8] | -0.43 ± 0.282 [8] | 0.78 ± 0.391 [8] | 0.527 |
| **BW Day 15-1 g** | 0.67 ± 0.231 [8] | 1.10 ± 0.465 [8] | 1.46 ± 0.369 [8] | 2.27 ± 0.861 [8] | 0.67 ± 0.421 [8] | 1.36 ± 0.368 [8] | 0.357 |
| **BW Day 22-1 g** | 1.12 ± 0.123 [8] | 1.13 ± 0.328 [8] | 2.56 ± 0.659 [8]\* | 1.13 ± 0.234 [8] | 1.10 ± 0.459 [8] | 1.67 ± 0.259 [8] | 0.230 |
| **BW Day 29-1 g** | 2.07 ± 0.659 [8] | 1.71 ± 0.327 [8] | 2.64 ± 0.619 [8] | 2.04 ± 0.232 [8] | 1.71 ± 0.454 [8] | 2.58 ± 0.374 [8] | 0.406 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 21.15 ± 0.429 [8] | 22.38 ± 0.772 [8] | 0.115 |
| **Body Weight Day 8 g** | 21.76 ± 0.397 [8] | 23.51 ± 1.078 [8] | 0.208 |
| **Body Weight Day 15 g** | 21.82 ± 0.394 [8] | 23.49 ± 0.949 [8] | 0.156 |
| **Body Weight Day 22 g** | 22.27 ± 0.398 [8] | 24.50 ± 1.218 [8] | 0.115 |
| **Body Weight Day 29 g** | 23.23 ± 0.487 [8] | 23.88 ± 1.086 [8] | 0.294 |
| **BW Day 8-1 g** | 0.60 ± 0.198 [8] | 1.13 ± 0.396 [8] | 0.462 |
| **BW Day 15-1 g** | 0.67 ± 0.231 [8] | 1.11 ± 0.267 [8] | 0.294 |
| **BW Day 22-1 g** | 1.12 ± 0.123 [8] | 2.12 ± 0.488 [8] | 0.074 |
| **BW Day 29-1 g** | 2.07 ± 0.659 [8] | 1.50 ± 0.380 [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 Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 BODY WEIGHTS IN FEMALE MICE  STUDY 2** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 21.26 ± 0.511 [8] | 21.29 ± 0.338 [8] | 21.10 ± 0.528 [8] | 22.22 ± 0.468 [8] | 22.28 ± 0.639 [8] | 21.84 ± 0.473 [8] | 0.125 |
| **Body Weight Day 8 g** | 21.44 ± 0.380 [8] | 21.98 ± 0.536 [8] | 20.99 ± 0.579 [8] | 22.81 ± 0.537 [8] | 22.71 ± 0.626 [8] | 22.55 ± 0.519 [8] | 0.029 |
| **Body Weight Day 15 g** | 21.83 ± 0.380 [8] | 22.58 ± 0.607 [8] | 21.82 ± 0.543 [8] | 22.60 ± 0.425 [8] | 23.39 ± 0.727 [8] | 23.00 ± 0.525 [8] | 0.065 |
| **Body Weight Day 22 g** | 22.09 ± 0.486 [8] | 22.86 ± 0.712 [8] | 22.07 ± 0.422 [8] | 23.90 ± 0.463 [8] | 23.59 ± 0.665 [8] | 23.57 ± 0.465 [8] | 0.009 |
| **Body Weight Day 29 g** | 23.48 ± 0.635 [8] | 23.82 ± 0.772 [8] | 23.61 ± 0.622 [8] | 24.47 ± 0.582 [8] | 24.51 ± 0.834 [8] | 24.16 ± 0.509 [8] | 0.248 |
| **BW Day 8-1 g** | 0.19 ± 0.364 [8] | 0.68 ± 0.297 [8] | -0.11 ± 0.197 [8] | 0.59 ± 0.175 [8] | 0.43 ± 0.182 [8] | 0.71 ± 0.162 [8] | 0.251 |
| **BW Day 15-1 g** | 0.57 ± 0.265 [8] | 1.29 ± 0.387 [8] | 0.73 ± 0.145 [8] | 0.39 ± 0.349 [8] | 1.11 ± 0.314 [8] | 1.17 ± 0.175 [8] | 0.263 |
| **BW Day 22-1 g** | 0.83 ± 0.479 [8] | 1.57 ± 0.447 [8] | 0.97 ± 0.182 [8] | 1.69 ± 0.304 [8] | 1.32 ± 0.248 [8] | 1.74 ± 0.283 [8] | 0.047 |
| **BW Day 29-1 g** | 2.22 ± 0.554 [8] | 2.53 ± 0.485 [8] | 2.51 ± 0.342 [8] | 2.25 ± 0.391 [8] | 2.23 ± 0.386 [8] | 2.32 ± 0.137 [8] | 0.632 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 21.26 ± 0.511 [8] | 21.61 ± 0.493 [8] | 0.916 |
| **Body Weight Day 8 g** | 21.44 ± 0.380 [8] | 22.88 ± 0.753 [8] | 0.345 |
| **Body Weight Day 15 g** | 21.83 ± 0.380 [8] | 23.52 ± 0.559 [8]\* | 0.027 |
| **Body Weight Day 22 g** | 22.09 ± 0.486 [8] | 23.99 ± 0.990 [8] | 0.208 |
| **Body Weight Day 29 g** | 23.48 ± 0.635 [8] | 23.35 ± 0.995 [8] | 0.752 |
| **BW Day 8-1 g** | 0.19 ± 0.364 [8] | 1.27 ± 0.323 [8]\* | 0.093 |
| **BW Day 15-1 g** | 0.57 ± 0.265 [8] | 1.91 ± 0.257 [8]\*\* | 0.003 |
| **BW Day 22-1 g** | 0.83 ± 0.479 [8] | 2.38 ± 0.561 [8] | 0.059 |
| **BW Day 29-1 g** | 2.22 ± 0.554 [8] | 1.74 ± 0.515 [8] | 0.600 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 5 PFDA DELAYED TYPE HYPERSENSITIVITY IN FEMALE MICE  STUDY 3** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **24 Hr Swelling (mm\*100)** | 83.50 ± 9.359 [8] | 85.44 ± 5.567 [8] | 79.19 ± 5.524 [8] | 88.50 ± 10.53 [8] | 64.13 ± 7.170 [8] | 74.56 ± 10.02 [8] | 0.164 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **24 Hr Swelling (mm\*100)** | 83.50 ± 9.359 [8] | 9.81 ± 2.842 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **Challenge Only** | **Trendc** |
| --- | --- | --- | --- |
| **24 Hr Swelling (mm\*100)** | 83.50 ± 9.359 [8] | 7.75 ± 1.790 [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 6 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 3** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 21.21 ± 0.492 [8] | 21.24 ± 0.462 [8] | 20.79 ± 0.446 [8] | 21.43 ± 0.444 [8] | 21.59 ± 0.368 [8] | 21.33 ± 0.309 [8] | 0.376 |
| **Body Weight Day 8 g** | 21.71 ± 0.468 [8] | 22.33 ± 0.436 [8] | 21.07 ± 0.488 [8] | 21.74 ± 0.454 [8] | 21.93 ± 0.344 [8] | 21.89 ± 0.308 [8] | 0.557 |
| **Body Weight Day 15 g** | 22.36 ± 0.576 [8] | 22.91 ± 0.592 [8] | 21.70 ± 0.462 [8] | 22.35 ± 0.450 [8] | 22.54 ± 0.321 [8] | 22.75 ± 0.393 [8] | 0.357 |
| **Body Weight Day 22 g** | 22.19 ± 0.469 [8] | 23.60 ± 0.677 [8] | 21.80 ± 0.532 [8] | 22.22 ± 0.581 [8] | 22.33 ± 0.427 [8] | 22.24 ± 0.369 [8] | 0.632 |
| **Body Weight Day 29 g** | 23.80 ± 0.657 [8] | 24.87 ± 0.488 [8] | 23.04 ± 0.630 [8] | 23.33 ± 0.585 [8] | 24.00 ± 0.425 [8] | 23.40 ± 0.368 [8] | 0.381 |
| **BW Day 8-1 g** | 0.50 ± 0.215 [8] | 1.09 ± 0.246 [8] | 0.28 ± 0.122 [8] | 0.31 ± 0.211 [8] | 0.34 ± 0.326 [8] | 0.56 ± 0.176 [8] | 0.283 |
| **BW Day 15-1 g** | 1.15 ± 0.201 [8] | 1.67 ± 0.300 [8] | 0.92 ± 0.121 [8] | 0.92 ± 0.122 [8] | 0.96 ± 0.318 [8] | 1.42 ± 0.362 [8] | 0.432 |
| **BW Day 22-1 g** | 0.98 ± 0.648 [8] | 2.36 ± 0.297 [8] | 1.69 ± 0.644 [8] | 0.79 ± 0.338 [8] | 0.74 ± 0.380 [8] | 0.91 ± 0.302 [8] | 0.184 |
| **BW Day 29-1 g** | 2.58 ± 0.920 [8] | 3.63 ± 0.214 [8] | 2.25 ± 0.245 [8] | 1.80 ± 0.259 [8] | 2.41 ± 0.286 [8] | 2.06 ± 0.287 [8] | 0.043 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 21.21 ± 0.492 [8] | 21.63 ± 0.503 [8] | 0.529 |
| **Body Weight Day 8 g** | 21.71 ± 0.468 [8] | 22.12 ± 0.653 [8] | 0.834 |
| **Body Weight Day 15 g** | 22.36 ± 0.576 [8] | 22.64 ± 0.865 [8] | 1.000 |
| **Body Weight Day 22 g** | 22.19 ± 0.469 [8] | 22.72 ± 0.744 [8] | 0.916 |
| **Body Weight Day 29 g** | 23.80 ± 0.657 [8] | 22.98 ± 0.788 [8] | 0.345 |
| **BW Day 8-1 g** | 0.50 ± 0.215 [8] | 0.49 ± 0.257 [8] | 0.916 |
| **BW Day 15-1 g** | 1.15 ± 0.201 [8] | 1.01 ± 0.479 [8] | 0.345 |
| **BW Day 22-1 g** | 0.98 ± 0.648 [8] | 1.09 ± 0.335 [8] | 1.000 |
| **BW Day 29-1 g** | 2.58 ± 0.920 [8] | 1.34 ± 0.376 [8] | 0.248 |

| **TABLE 6 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **Challenge Only** | **Trendc** |
| **Body Weight Day 1 g** | 21.21 ± 0.492 [8] | 21.29 ± 0.367 [8] | 0.674 |
| **Body Weight Day 8 g** | 21.71 ± 0.468 [8] | 20.92 ± 0.395 [8] | 0.345 |
| **Body Weight Day 15 g** | 22.36 ± 0.576 [8] | 21.53 ± 0.450 [8] | 0.318 |
| **Body Weight Day 22 g** | 22.19 ± 0.469 [8] | 21.59 ± 0.457 [8] | 0.462 |
| **Body Weight Day 29 g** | 23.80 ± 0.657 [8] | 22.87 ± 0.417 [8] | 0.189 |
| **BW Day 8-1 g** | 0.50 ± 0.215 [8] | -0.37 ± 0.204 [8]\* | 0.016 |
| **BW Day 15-1 g** | 1.15 ± 0.201 [8] | 0.24 ± 0.412 [8] | 0.093 |
| **BW Day 22-1 g** | 0.98 ± 0.648 [8] | 0.30 ± 0.227 [8] | 0.345 |
| **BW Day 29-1 g** | 2.58 ± 0.920 [8] | 1.58 ± 0.203 [8] | 0.462 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 7 PFDA T-DEPENDENT IGM ANTIBODY RESPONSE IN FEMALE MICE  STUDY 4** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **IgM PFC/10^6 spleen cells** | 1492.7 ± 133.0 [8] | 1340.5 ± 144.2 [8] | 1591.5 ± 210.1 [8] | 1638.6 ± 110.2 [8] | 1671.0 ± 97.65 [8] | 1323.3 ± 128.0 [8] | 0.986 |
| **IgM PFC/spleen (X 10^3)** | 308.59 ± 20.66 [8] | 259.54 ± 40.29 [8] | 307.91 ± 44.69 [8] | 305.25 ± 26.10 [8] | 339.53 ± 17.10 [8] | 228.60 ± 20.91 [8] | 0.607 |
| **Cells/ spleen (X 10^7)** | 20.99 ± 0.886 [8] | 18.79 ± 1.365 [8] | 20.45 ± 1.693 [8] | 18.54 ± 0.605 [8] | 20.48 ± 0.777 [8] | 17.43 ± 0.659 [8] | 0.191 |
| **Spleen Weight** | 81.25 ± 3.797 [8] | 76.25 ± 5.706 [8] | 100.38 ± 15.91 [8] | 87.38 ± 2.927 [8] | 82.25 ± 2.484 [8] | 70.75 ± 2.889 [8] | 0.458 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **IgM PFC/10^6 spleen cells** | 1492.7 ± 133.0 [8] | 1.20 ± 0.272 [8]\*\* | <.001 |
| **IgM PFC/spleen (X 10^3)** | 308.59 ± 20.66 [8] | 0.09 ± 0.018 [8]\*\* | <.001 |
| **Cells/ spleen (X 10^7)** | 20.99 ± 0.886 [8] | 7.49 ± 0.402 [8]\*\* | <.001 |
| **Spleen Weight** | 81.25 ± 3.797 [8] | 42.00 ± 2.598 [8]\*\* | <.001 |

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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 Williams’ test when a trend was present (P < .01 from Jonckheere’s trend test)   or with Dunnett’s 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 Dunn’s 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 8 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 4** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 21.33 ± 0.378 [8] | 20.72 ± 0.250 [8] | 20.92 ± 0.499 [8] | 20.41 ± 0.266 [8] | 20.27 ± 0.213 [8] | 21.04 ± 0.273 [8] | 0.443 |
| **Body Weight Day 8 g** | 22.09 ± 0.323 [8] | 21.22 ± 0.226 [8] | 20.82 ± 0.763 [8] | 20.62 ± 0.366 [8] | 21.13 ± 0.252 [8] | 21.68 ± 0.290 [8] | 0.381 |
| **Body Weight Day 15 g** | 22.41 ± 0.544 [8] | 21.71 ± 0.294 [8] | 21.67 ± 0.592 [8] | 21.07 ± 0.354 [8] | 21.40 ± 0.219 [8] | 22.20 ± 0.256 [8] | 0.793 |
| **Body Weight Day 22 g** | 23.13 ± 0.506 [8] | 22.20 ± 0.421 [8] | 22.62 ± 0.765 [8] | 22.58 ± 0.344 [8] | 21.73 ± 0.295 [8] | 22.76 ± 0.245 [8] | 0.899 |
| **Body Weight Day 29 g** | 23.73 ± 0.603 [8] | 22.98 ± 0.322 [8] | 23.33 ± 0.806 [8] | 22.46 ± 0.372 [8] | 22.06 ± 0.213 [8] | 23.40 ± 0.346 [8] | 0.338 |
| **BW Day 8-1 g** | 0.77 ± 0.250 [8] | 0.50 ± 0.210 [8] | -0.10 ± 0.379 [8] | 0.21 ± 0.137 [8] | 0.86 ± 0.186 [8] | 0.65 ± 0.288 [8] | 0.773 |
| **BW Day 15-1 g** | 1.08 ± 0.350 [8] | 0.99 ± 0.194 [8] | 0.54 ± 0.212 [8] | 0.67 ± 0.151 [8] | 1.13 ± 0.198 [8] | 1.16 ± 0.264 [8] | 0.510 |
| **BW Day 22-1 g** | 1.80 ± 0.402 [8] | 1.48 ± 0.279 [8] | 1.69 ± 0.314 [8] | 2.18 ± 0.149 [8] | 1.46 ± 0.274 [8] | 1.73 ± 0.163 [8] | 0.745 |
| **BW Day 29-1 g** | 2.41 ± 0.358 [8] | 2.26 ± 0.189 [8] | 2.41 ± 0.395 [8] | 2.06 ± 0.243 [8] | 1.79 ± 0.212 [8] | 2.36 ± 0.312 [8] | 0.371 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 21.33 ± 0.378 [8] | 21.19 ± 0.428 [8] | 0.753 |
| **Body Weight Day 8 g** | 22.09 ± 0.323 [8] | 21.88 ± 0.482 [8] | 0.916 |
| **Body Weight Day 15 g** | 22.41 ± 0.544 [8] | 22.37 ± 0.481 [8] | 0.916 |
| **Body Weight Day 22 g** | 23.13 ± 0.506 [8] | 23.44 ± 0.608 [8] | 1.000 |
| **Body Weight Day 29 g** | 23.73 ± 0.603 [8] | 22.72 ± 0.614 [8] | 0.141 |
| **BW Day 8-1 g** | 0.77 ± 0.250 [8] | 0.68 ± 0.310 [8] | 0.462 |
| **BW Day 15-1 g** | 1.08 ± 0.350 [8] | 1.18 ± 0.223 [8] | 1.000 |
| **BW Day 22-1 g** | 1.80 ± 0.402 [8] | 2.25 ± 0.324 [8] | 0.345 |
| **BW Day 29-1 g** | 2.41 ± 0.358 [8] | 1.53 ± 0.264 [8] | 0.074 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 9 PFDA DNA SYNTHESIS IN FEMALE MICE  STUDY 5** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Cells/ femur (X10^6)** | 9.70 ± 0.651 [8] | 9.36 ± 0.344 [8] | 8.18 ± 0.705 [8] | 9.35 ± 0.558 [8] | 9.97 ± 0.860 [8] | 10.04 ± 1.088 [8] | 0.899 |
| **DNA Synth. CPM (avg of 3 repl)** | 84457 ± 2935 [8] | 76796 ± 3895 [8] | 83150 ± 7304 [8] | 71971 ± 4811 [8] | 82535 ± 4793 [8] | 79777 ± 2072 [8] | 0.732 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Cells/ femur (X10^6)** | 9.70 ± 0.651 [8] | 5.17 ± 0.461 [8]\*\* | 0.001 |
| **DNA Synth. CPM (avg of 3 repl)** | 84457 ± 2935 [8] | 76151 ± 6449 [8] | 0.294 |

|  |
| --- |
| 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 10 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 5** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 22.48 ± 0.360 [8] | 22.47 ± 0.374 [8] | 22.67 ± 0.288 [8] | 22.64 ± 0.434 [8] | 22.70 ± 0.377 [8] | 22.48 ± 0.505 [8] | 0.645 |
| **Body Weight Day 8 g** | 22.94 ± 0.364 [8] | 23.46 ± 0.446 [8] | 23.25 ± 0.508 [8] | 23.82 ± 0.549 [8] | 23.09 ± 0.268 [8] | 23.43 ± 0.515 [8] | 0.601 |
| **Body Weight Day 15 g** | 24.15 ± 0.475 [8] | 24.35 ± 0.382 [8] | 23.93 ± 0.606 [8] | 25.03 ± 0.601 [8] | 24.25 ± 0.452 [8] | 24.31 ± 0.684 [8] | 0.899 |
| **Body Weight Day 22 g** | 24.81 ± 0.617 [8] | 24.91 ± 0.535 [8] | 24.45 ± 0.748 [8] | 25.58 ± 0.632 [8] | 24.48 ± 0.590 [8] | 24.41 ± 0.458 [8] | 0.527 |
| **Body Weight Day 29 g** | 25.52 ± 0.674 [8] | 25.77 ± 0.358 [8] | 24.49 ± 0.519 [8] | 25.81 ± 0.831 [8] | 24.56 ± 0.492 [8] | 25.00 ± 0.749 [8] | 0.396 |
| **BW Day 8-1 g** | 0.45 ± 0.258 [8] | 1.00 ± 0.158 [8] | 0.57 ± 0.389 [8] | 1.18 ± 0.223 [8] | 0.39 ± 0.205 [8] | 0.95 ± 0.275 [8] | 0.600 |
| **BW Day 15-1 g** | 1.67 ± 0.289 [8] | 1.89 ± 0.185 [8] | 1.26 ± 0.414 [8] | 2.39 ± 0.338 [8] | 1.55 ± 0.300 [8] | 1.83 ± 0.446 [8] | 0.914 |
| **BW Day 22-1 g** | 2.32 ± 0.470 [8] | 2.44 ± 0.408 [8] | 1.77 ± 0.592 [8] | 2.94 ± 0.420 [8] | 1.78 ± 0.321 [8] | 1.93 ± 0.505 [8] | 0.267 |
| **BW Day 29-1 g** | 3.04 ± 0.533 [8] | 3.30 ± 0.147 [8] | 1.81 ± 0.294 [8] | 3.17 ± 0.520 [8] | 1.86 ± 0.399 [8] | 2.52 ± 0.553 [8] | 0.139 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 22.48 ± 0.360 [8] | 22.41 ± 0.493 [8] | 0.916 |
| **Body Weight Day 8 g** | 22.94 ± 0.364 [8] | 23.28 ± 0.598 [8] | 0.753 |
| **Body Weight Day 15 g** | 24.15 ± 0.475 [8] | 23.58 ± 0.619 [8] | 0.529 |
| **Body Weight Day 22 g** | 24.81 ± 0.617 [8] | 23.95 ± 0.611 [8] | 0.294 |
| **Body Weight Day 29 g** | 25.52 ± 0.674 [8] | 23.25 ± 0.683 [8]\* | 0.059 |
| **BW Day 8-1 g** | 0.45 ± 0.258 [8] | 0.86 ± 0.286 [8] | 0.462 |
| **BW Day 15-1 g** | 1.67 ± 0.289 [8] | 1.17 ± 0.248 [8] | 0.115 |
| **BW Day 22-1 g** | 2.32 ± 0.470 [8] | 1.54 ± 0.352 [8] | 0.141 |
| **BW Day 29-1 g** | 3.04 ± 0.533 [8] | 0.84 ± 0.471 [8]\* | 0.010 |

| **TABLE 10 (continued)** | | | |
| --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **AAGM1 1/10** | **Trendc** |
| **Body Weight Day 1 g** | 22.48 ± 0.360 [8] | 22.58 ± 0.384 [8] | 0.916 |
| **Body Weight Day 8 g** | 22.94 ± 0.364 [8] | 23.47 ± 0.596 [8] | 0.462 |
| **Body Weight Day 15 g** | 24.15 ± 0.475 [8] | 24.36 ± 0.548 [8] | 0.753 |
| **Body Weight Day 22 g** | 24.81 ± 0.617 [8] | 24.14 ± 0.696 [8] | 0.529 |
| **Body Weight Day 29 g** | 25.52 ± 0.674 [8] | 25.59 ± 0.586 [8] | 0.834 |
| **BW Day 8-1 g** | 0.45 ± 0.258 [8] | 0.89 ± 0.331 [8] | 0.172 |
| **BW Day 15-1 g** | 1.67 ± 0.289 [8] | 1.78 ± 0.492 [8] | 0.674 |
| **BW Day 22-1 g** | 2.32 ± 0.470 [8] | 1.56 ± 0.502 [8] | 0.294 |
| **BW Day 29-1 g** | 3.04 ± 0.533 [8] | 3.01 ± 0.356 [8] | 0.916 |

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| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 11 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 6a** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 23.12 ± 0.387 [12] |  |  | 23.53 ± 0.349 [12] | 23.03 ± 0.439 [12] | 23.42 ± 0.334 [12] | 0.811 |
| **Body Weight Day 8 g** | 24.07 ± 0.552 [12] |  |  | 24.26 ± 0.450 [12] | 24.24 ± 0.482 [12] | 23.89 ± 0.317 [12] | 0.832 |
| **Body Weight Day 15 g** | 24.24 ± 0.532 [12] |  |  | 24.53 ± 0.361 [12] | 24.52 ± 0.623 [12] | 24.45 ± 0.449 [12] | 0.934 |
| **Body Weight Day 22 g** | 23.95 ± 0.506 [12] |  |  | 24.61 ± 0.342 [12] | 24.78 ± 0.574 [12] | 24.45 ± 0.322 [12] | 0.353 |
| **Body Weight Day 29 g** | 25.24 ± 0.453 [12] |  |  | 26.03 ± 0.473 [12] | 25.41 ± 0.523 [12] | 24.71 ± 0.330 [12] | 0.286 |
| **BW Day 8-1 g** | 0.96 ± 0.316 [12] |  |  | 0.73 ± 0.197 [12] | 1.21 ± 0.234 [12] | 0.48 ± 0.233 [12] | 0.513 |
| **BW Day 15-1 g** | 1.12 ± 0.297 [12] |  |  | 1.01 ± 0.319 [12] | 1.49 ± 0.381 [12] | 1.03 ± 0.275 [12] | 0.861 |
| **BW Day 22-1 g** | 0.84 ± 0.312 [12] |  |  | 0.85 ± 0.307 [12] | 1.76 ± 0.304 [12] | 1.03 ± 0.279 [12] | 0.242 |
| **BW Day 29-1 g** | 2.13 ± 0.353 [12] |  |  | 2.51 ± 0.303 [12] | 2.38 ± 0.264 [12] | 1.29 ± 0.300 [12] | 0.025 |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 23.12 ± 0.387 [12] | 23.68 ± 0.401 [12] | 0.299 |
| **Body Weight Day 8 g** | 24.07 ± 0.552 [12] | 23.91 ± 0.632 [12] | 0.908 |
| **Body Weight Day 15 g** | 24.24 ± 0.532 [12] | 24.52 ± 0.534 [12] | 0.644 |
| **Body Weight Day 22 g** | 23.95 ± 0.506 [12] | 24.80 ± 0.499 [12] | 0.273 |
| **Body Weight Day 29 g** | 25.24 ± 0.453 [12] | 22.53 ± 0.539 [12]\*\* | 0.002 |
| **BW Day 8-1 g** | 0.96 ± 0.316 [12] | 0.23 ± 0.355 [12] | 0.065 |
| **BW Day 15-1 g** | 1.12 ± 0.297 [12] | 0.84 ± 0.376 [12] | 0.603 |
| **BW Day 22-1 g** | 0.84 ± 0.312 [12] | 1.12 ± 0.376 [12] | 0.419 |
| **BW Day 29-1 g** | 2.13 ± 0.353 [12] | -1.15 ± 0.379 [12]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 BODY WEIGHTS IN FEMALE MICE  STUDY 6b** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1** | 23.25 ± 0.430 [12] |  |  | 22.74 ± 0.458 [12] | 23.28 ± 0.320 [12] | 22.91 ± 0.411 [12] | 0.733 |
| **Body Weight Day 8** | 23.54 ± 0.567 [12] |  |  | 23.40 ± 0.571 [12] | 23.93 ± 0.435 [12] | 23.37 ± 0.417 [12] | 0.905 |
| **Body Weight Day 15** | 24.23 ± 0.689 [12] |  |  | 24.18 ± 0.628 [12] | 23.94 ± 0.482 [11] | 23.50 ± 0.443 [12] | 0.459 |
| **Body Weight Day 22** | 24.87 ± 0.807 [12] |  |  | 24.96 ± 0.673 [12] | 24.87 ± 0.447 [11] | 23.84 ± 0.517 [12] | 0.482 |
| **Body Weight Day 29 g** | 25.72 ± 1.015 [12] |  |  | 25.82 ± 0.840 [12] | 25.14 ± 0.527 [11] | 23.89 ± 0.482 [12] | 0.141 |
| **BW Day 8-1** | 0.29 ± 0.502 [12] |  |  | 0.66 ± 0.239 [12] | 0.64 ± 0.291 [12] | 0.46 ± 0.162 [12] | 0.775 |
| **BW Day 15-1** | 0.98 ± 0.639 [12] |  |  | 1.45 ± 0.278 [12] | 0.77 ± 0.297 [11] | 0.59 ± 0.274 [12] | 0.271 |
| **BW Day 22-1** | 1.62 ± 0.709 [12] |  |  | 2.23 ± 0.432 [12] | 1.70 ± 0.356 [11] | 0.93 ± 0.351 [12] | 0.431 |
| **BW Day 29-1** | 2.47 ± 0.900 [12] |  |  | 3.08 ± 0.537 [12] | 1.97 ± 0.454 [11] | 0.98 ± 0.297 [12] | 0.086 |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1** | 23.25 ± 0.430 [12] | 22.06 ± 0.260 [12]\* | 0.028 |
| **Body Weight Day 8** | 23.54 ± 0.567 [12] | 22.62 ± 0.290 [12] | 0.326 |
| **Body Weight Day 15** | 24.23 ± 0.689 [12] | 22.86 ± 0.331 [12] | 0.133 |
| **Body Weight Day 22** | 24.87 ± 0.807 [12] | 23.52 ± 0.419 [12] | 0.184 |
| **Body Weight Day 29 g** | 25.72 ± 1.015 [12] | 21.28 ± 0.285 [12]\*\* | <.001 |
| **BW Day 8-1** | 0.29 ± 0.502 [12] | 0.57 ± 0.159 [12] | 0.525 |
| **BW Day 15-1** | 0.98 ± 0.639 [12] | 0.80 ± 0.262 [12] | 0.954 |
| **BW Day 22-1** | 1.62 ± 0.709 [12] | 1.47 ± 0.377 [12] | 0.795 |
| **BW Day 29-1** | 2.47 ± 0.900 [12] | -0.78 ± 0.262 [12]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 13 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 6c** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 23.22 ± 0.191 [12] |  |  | 22.49 ± 0.371 [12] | 23.07 ± 0.429 [12] | 22.10 ± 0.383 [12] | 0.046 |
| **Body Weight Day 8 g** | 24.38 ± 0.239 [12] |  |  | 23.52 ± 0.463 [12] | 23.45 ± 0.537 [12] | 22.76 ± 0.316 [12]\*\* | 0.008 |
| **Body Weight Day 15 g** | 24.14 ± 0.306 [12] |  |  | 23.63 ± 0.476 [12] | 24.20 ± 0.562 [12] | 23.23 ± 0.454 [12] | 0.156 |
| **Body Weight Day 22 g** | 24.18 ± 0.361 [12] |  |  | 24.24 ± 0.532 [12] | 24.38 ± 0.594 [12] | 23.21 ± 0.456 [12] | 0.162 |
| **Body Weight Day 29 g** | 25.66 ± 0.356 [12] |  |  | 24.62 ± 0.455 [12] | 25.20 ± 0.638 [12] | 23.72 ± 0.497 [12]\* | 0.016 |
| **BW Day 8-1 g** | 1.15 ± 0.299 [12] |  |  | 1.03 ± 0.161 [12] | 0.38 ± 0.193 [12]\* | 0.66 ± 0.166 [12] | 0.051 |
| **BW Day 15-1 g** | 0.92 ± 0.302 [12] |  |  | 1.15 ± 0.242 [12] | 1.13 ± 0.208 [12] | 1.13 ± 0.217 [12] | 0.525 |
| **BW Day 22-1 g** | 0.96 ± 0.370 [12] |  |  | 1.75 ± 0.300 [12] | 1.32 ± 0.282 [12] | 1.11 ± 0.178 [12] | 0.782 |
| **BW Day 29-1 g** | 2.43 ± 0.323 [12] |  |  | 2.13 ± 0.181 [12] | 2.13 ± 0.299 [12] | 1.62 ± 0.263 [12] | 0.036 |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 23.22 ± 0.191 [12] | 23.30 ± 0.351 [12] | 0.817 |
| **Body Weight Day 8 g** | 24.38 ± 0.239 [12] | 23.19 ± 0.336 [12]\*\* | 0.008 |
| **Body Weight Day 15 g** | 24.14 ± 0.306 [12] | 23.95 ± 0.393 [12] | 0.862 |
| **Body Weight Day 22 g** | 24.18 ± 0.361 [12] | 24.04 ± 0.434 [12] | 1.000 |
| **Body Weight Day 29 g** | 25.66 ± 0.356 [12] | 22.41 ± 0.342 [12]\*\* | <.001 |
| **BW Day 8-1 g** | 1.15 ± 0.299 [12] | -0.10 ± 0.250 [12]\*\* | 0.005 |
| **BW Day 15-1 g** | 0.92 ± 0.302 [12] | 0.65 ± 0.188 [12] | 0.564 |
| **BW Day 22-1 g** | 0.96 ± 0.370 [12] | 0.74 ± 0.388 [12] | 0.453 |
| **BW Day 29-1 g** | 2.43 ± 0.323 [12] | -0.89 ± 0.350 [12]\*\* | <.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 14 PFDA SURVIVAL IN FEMALE MICE  STUDY 6a** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **# Living** | 12 |  |  | 12 | 12 | 12 | 1.000 |
| **# Dead** | 0 |  |  | 0 | 0 | 0 |  |
| **% Moribundity (N=12)** | 0 |  |  | 0 | 0 | 0 |  |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **# Living** | 12 | 10 | 0.478 |
| **# Dead** | 0 | 2 |  |
| **% Moribundity (N=12)** | 0 | 17 |  |

|  |
| --- |
| a: Values shown are number of animals for the given category, or percent of animals dead at end of study.  b: Trend test was calculated using Cochran-Armitage test. Each dose was compared to the control using Fisher’s Exact test.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 15 PFDA SURVIVAL IN FEMALE MICE  STUDY 6b** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **# Living** | 9 |  |  | 8 | 7 | 10 | 0.933 |
| **# Dead** | 3 |  |  | 4 | 4 | 2 |  |
| **% Moribundity (N=12)** | 25 |  |  | 33 | 36 | 17 |  |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **# Living** | 9 | 2 \* | 0.012 |
| **# Dead** | 3 | 10 |  |
| **% Moribundity (N=12)** | 25 | 83 |  |

|  |
| --- |
| a: Values shown are number of animals for the given category, or percent of animals dead at end of study.  b: Trend test was calculated using Cochran-Armitage test. Each dose was compared to the control using Fisher’s Exact test.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 16 PFDA SURVIVAL IN FEMALE MICE  STUDY 6c** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **# Living** | 7 |  |  | 6 | 7 | 5 | 0.596 |
| **# Dead** | 5 |  |  | 6 | 5 | 7 |  |
| **% Moribundity (N=12)** | 42 |  |  | 50 | 42 | 58 |  |

| **Parametera** | **Vehicle Control** | **AZA 200 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **# Living** | 7 | 0 \*\* | 0.005 |
| **# Dead** | 5 | 12 |  |
| **% Moribundity (N=12)** | 42 | 100 |  |

|  |
| --- |
| a: Values shown are number of animals for the given category, or percent of animals dead at end of study.  b: Trend test was calculated using Cochran-Armitage test. Each dose was compared to the control using Fisher’s Exact test.  [\* = P<0.05, \*\* = P<0.01] |

| **TABLE 17 PFDA NATURAL KILLER ASSAY IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Spleen weight mg** | 66.25 ± 3.115 [8] | 66.50 ± 4.062 [8] | 65.00 ± 2.079 [8] | 68.63 ± 2.220 [8] | 68.50 ± 4.119 [8] | 59.75 ± 2.776 [8] | 0.411 |
| **Spleen total cells X 10^7** | 14.94 ± 0.654 [8] | 14.71 ± 0.742 [8] | 13.81 ± 0.685 [8] | 12.94 ± 0.504 [8] | 13.75 ± 1.056 [8] | 11.39 ± 0.524 [8]\*\* | <.001 |
| **NK 200:1** | 16.49 ± 4.000 [8] | 15.85 ± 3.312 [8] | 12.95 ± 3.030 [8] | 17.05 ± 4.502 [8] | 18.05 ± 5.101 [8] | 21.29 ± 4.896 [8] | 0.481 |
| **NK 100:1** | 11.69 ± 3.056 [8] | 11.44 ± 2.749 [8] | 8.80 ± 2.668 [8] | 13.96 ± 3.683 [8] | 12.60 ± 3.488 [8] | 17.53 ± 3.127 [8] | 0.223 |
| **NK 50:1** | 8.50 ± 2.166 [8] | 8.82 ± 2.021 [8] | 6.39 ± 1.754 [8] | 8.57 ± 3.186 [8] | 9.42 ± 2.773 [8] | 11.35 ± 2.628 [8] | 0.652 |
| **NK 25:1** | 4.23 ± 1.631 [8] | 4.78 ± 1.787 [8] | 4.04 ± 1.708 [8] | 4.39 ± 2.246 [8] | 4.92 ± 2.434 [8] | 7.33 ± 2.366 [8] | 0.576 |
| **NK 12.5:1** | 1.50 ± 1.504 [8] | 1.50 ± 1.569 [8] | 1.45 ± 1.353 [8] | 1.52 ± 1.638 [8] | 1.55 ± 1.678 [8] | 4.98 ± 2.146 [8] | 0.241 |
| **NK 6.25:1** | 1.46 ± 2.307 [8] | 0.39 ± 1.217 [8] | 0.25 ± 0.947 [8] | -0.24 ± 1.497 [8] | 0.20 ± 1.417 [8] | 2.19 ± 1.540 [8] | 0.570 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Spleen total cells X 10^7** | 14.94 ± 0.654 [8] | 4.74 ± 0.449 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **AAGM1 1/10** | **Trendc** |
| --- | --- | --- | --- |
| **Spleen weight mg** | 66.25 ± 3.115 [8] | 83.86 ± 3.074 [7]\*\* | 0.004 |
| **NK 200:1** | 16.49 ± 4.000 [8] | 0.21 ± 1.741 [8]\*\* | 0.002 |
| **NK 100:1** | 11.69 ± 3.056 [8] | 0.64 ± 1.440 [8]\*\* | 0.003 |
| **NK 50:1** | 8.50 ± 2.166 [8] | 0.46 ± 1.401 [8]\* | 0.016 |
| **NK 25:1** | 4.23 ± 1.631 [8] | -0.82 ± 1.387 [8] | 0.074 |
| **NK 12.5:1** | 1.50 ± 1.504 [8] | -0.36 ± 1.824 [8] | 0.142 |
| **NK 6.25:1** | 1.46 ± 2.307 [8] | 2.02 ± 3.251 [8] | 0.529 |

|  |
| --- |
| 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 18 PFDA MIXED LEUKOCYTE RESPONSE IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **MLR R** | 2023.8 ± 435.5 [8] | 2041.6 ± 272.0 [8] | 2400.3 ± 715.3 [8] | 2573.5 ± 455.2 [8] | 1607.4 ± 161.2 [8] | 1275.5 ± 169.5 [8] | 0.120 |
| **MLR R+S** | 55388 ± 16174 [8] | 57927 ± 14399 [8] | 58349 ± 13890 [8] | 65015 ± 18621 [8] | 74835 ± 19490 [8] | 67852 ± 18497 [8] | 0.516 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **MLR R** | 2023.8 ± 435.5 [8] | 892.00 ± 154.3 [8]\*\* | 0.005 |
| **MLR R+S** | 55388 ± 16174 [8] | 41771 ± 13997 [8] | 0.248 |

|  |
| --- |
| 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 ANTI-CD3 PROLIFERATION IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **aCD3 unstim** | 2928.8 ± 307.4 [8] | 3426.0 ± 174.8 [8] | 3688.0 ± 480.2 [8] | 4433.0 ± 959.7 [8] | 4322.0 ± 487.1 [8] | 3132.6 ± 413.0 [8] | 0.279 |
| **aCD3 stim** | 249603 ± 11663 [8] | 275463 ± 14183 [8] | 272030 ± 11389 [8] | 280357 ± 10507 [8] | 260946 ± 16032 [8] | 237083 ± 11164 [8] | 0.504 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **aCD3 unstim** | 2928.8 ± 307.4 [8] | 799.25 ± 139.2 [8]\*\* | <.001 |
| **aCD3 stim** | 249603 ± 11663 [8] | 72652 ± 3711 [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 20 PFDA BODY WEIGHTS IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 22.97 ± 0.553 [8] | 23.21 ± 0.419 [8] | 23.04 ± 0.535 [8] | 23.01 ± 0.592 [8] | 22.98 ± 0.451 [8] | 22.41 ± 0.404 [8] | 0.321 |
| **Body Weight Day 8 g** | 24.18 ± 0.626 [8] | 24.29 ± 0.637 [8] | 24.20 ± 0.711 [8] | 24.73 ± 0.693 [8] | 24.87 ± 0.502 [8] | 23.59 ± 0.418 [8] | 0.835 |
| **Body Weight Day 15 g** | 25.15 ± 0.752 [8] | 24.51 ± 0.582 [8] | 24.39 ± 0.788 [8] | 24.48 ± 0.808 [8] | 25.64 ± 0.631 [8] | 23.97 ± 0.551 [8] | 0.711 |
| **Body Weight Day 22 g** | 26.24 ± 0.930 [8] | 25.74 ± 0.737 [8] | 25.97 ± 0.755 [8] | 27.04 ± 1.012 [8] | 25.73 ± 0.710 [8] | 24.74 ± 0.545 [8] | 0.362 |
| **Body Weight Day 29 g** | 26.78 ± 0.921 [8] | 26.12 ± 0.897 [8] | 25.62 ± 0.771 [8] | 26.65 ± 1.114 [8] | 26.82 ± 0.866 [8] | 25.15 ± 0.456 [8] | 0.539 |
| **BW Day 8-1 g** | 1.21 ± 0.324 [8] | 1.08 ± 0.264 [8] | 1.16 ± 0.293 [8] | 1.72 ± 0.227 [8] | 1.89 ± 0.170 [8] | 1.18 ± 0.238 [8] | 0.203 |
| **BW Day 15-1 g** | 2.17 ± 0.426 [8] | 1.30 ± 0.282 [8] | 1.35 ± 0.409 [8] | 1.47 ± 0.372 [8] | 2.66 ± 0.329 [8] | 1.56 ± 0.311 [8] | 0.780 |
| **BW Day 22-1 g** | 3.27 ± 0.535 [8] | 2.53 ± 0.371 [8] | 2.93 ± 0.428 [8] | 4.03 ± 0.514 [8] | 2.74 ± 0.323 [8] | 2.33 ± 0.250 [8] | 0.386 |
| **BW Day 29-1 g** | 3.81 ± 0.531 [8] | 2.91 ± 0.556 [8] | 2.58 ± 0.418 [8] | 3.64 ± 0.585 [8] | 3.83 ± 0.504 [8] | 2.74 ± 0.276 [8] | 0.759 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 22.97 ± 0.553 [8] | 22.22 ± 0.536 [8] | 0.248 |
| **Body Weight Day 8 g** | 24.18 ± 0.626 [8] | 23.37 ± 0.532 [8] | 0.401 |
| **Body Weight Day 15 g** | 25.15 ± 0.752 [8] | 22.94 ± 0.577 [8]\* | 0.031 |
| **Body Weight Day 22 g** | 26.24 ± 0.930 [8] | 24.33 ± 0.750 [8] | 0.208 |
| **Body Weight Day 29 g** | 26.78 ± 0.921 [8] | 22.81 ± 0.527 [8]\*\* | 0.005 |
| **BW Day 8-1 g** | 1.21 ± 0.324 [8] | 1.15 ± 0.261 [8] | 0.834 |
| **BW Day 15-1 g** | 2.17 ± 0.426 [8] | 0.72 ± 0.298 [8]\* | 0.046 |
| **BW Day 22-1 g** | 3.27 ± 0.535 [8] | 2.10 ± 0.387 [8] | 0.115 |
| **BW Day 29-1 g** | 3.81 ± 0.531 [8] | 0.58 ± 0.400 [8]\*\* | 0.001 |

|  |
| --- |
| a: All values shown as mean ± standard error [number]  b: Each dose was compared to the control with Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 21 PFDA PERCENT SURFACE MARKERS IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **%Ig+** | 50.98 ± 1.070 [8] | 53.71 ± 0.899 [8] | 55.59 ± 0.676 [8]\* | 52.90 ± 0.525 [8] | 53.73 ± 1.077 [8] | 49.04 ± 0.914 [8] | 0.173 |
| **%CD3+** | 32.64 ± 0.757 [8] | 30.15 ± 0.776 [8] | 29.89 ± 0.948 [8] | 29.58 ± 0.901 [8] | 30.78 ± 1.008 [8] | 30.70 ± 1.103 [8] | 0.209 |
| **%CD4+ CD8-** | 20.86 ± 0.532 [8] | 18.91 ± 0.462 [8] | 19.61 ± 0.415 [8] | 19.64 ± 0.431 [8] | 20.06 ± 0.540 [8] | 19.55 ± 0.829 [8] | 0.492 |
| **%CD4- CD8+** | 11.53 ± 0.270 [8] | 10.49 ± 0.320 [8] | 9.99 ± 0.298 [8]\* | 10.33 ± 0.483 [8] | 11.35 ± 0.414 [8] | 10.91 ± 0.531 [8] | 0.698 |
| **%CD4+ CD8+** | 0.13 ± 0.016 [8] | 0.11 ± 0.023 [8] | 0.08 ± 0.016 [8] | 0.13 ± 0.025 [8] | 0.13 ± 0.016 [8] | 0.09 ± 0.013 [8] | 0.511 |
| **%NK1.1+ CD3-** | 4.58 ± 0.202 [8] | 3.98 ± 0.187 [8] | 4.24 ± 0.158 [8] | 4.39 ± 0.244 [8] | 4.13 ± 0.151 [8] | 4.89 ± 0.209 [8] | 0.356 |
| **%Mac3+** | 5.11 ± 0.181 [8] | 4.55 ± 0.353 [8] | 4.40 ± 0.207 [8]\* | 4.14 ± 0.231 [8]\*\* | 4.21 ± 0.161 [8]\*\* | 4.13 ± 0.178 [8]\*\* | 0.005 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **%Ig+** | 50.98 ± 1.070 [8] | 28.68 ± 1.611 [8]\*\* | <.001 |
| **%CD3+** | 32.64 ± 0.757 [8] | 57.13 ± 1.325 [8]\*\* | <.001 |
| **%CD4+ CD8-** | 20.86 ± 0.532 [8] | 32.06 ± 0.934 [8]\*\* | <.001 |
| **%CD4- CD8+** | 11.53 ± 0.270 [8] | 21.46 ± 0.697 [8]\*\* | <.001 |
| **%CD4+ CD8+** | 0.13 ± 0.016 [8] | 0.16 ± 0.026 [8] | 0.268 |
| **%NK1.1+ CD3-** | 4.58 ± 0.202 [8] | 2.64 ± 0.107 [8]\*\* | <.001 |
| **%Mac3+** | 5.11 ± 0.181 [8] | 4.41 ± 0.226 [8]\* | 0.026 |

| **Parametera** | **Vehicle Control** | **AAGM1 1/10** | **Trendc** |
| --- | --- | --- | --- |
| **%Ig+** | 50.98 ± 1.070 [8] | 21.80 ± . [1] | 0.121 |
| **%CD3+** | 32.64 ± 0.757 [8] | 31.06 ± 2.827 [7] | 0.247 |
| **%NK1.1+ CD3-** | 4.58 ± 0.202 [8] | 0.89 ± 0.180 [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 22 PFDA ABSOLUTE SURFACE MARKERS IN FEMALE MICE  STUDY 7** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **ABS Ig+** | 76.43 ± 4.696 [8] | 78.89 ± 3.791 [8] | 76.55 ± 3.321 [8] | 68.43 ± 2.682 [8] | 73.62 ± 5.330 [8] | 55.65 ± 2.088 [8]\*\* | <.001 |
| **ABS CD3+** | 48.73 ± 2.304 [8] | 44.33 ± 2.465 [8] | 41.50 ± 2.808 [8] | 38.16 ± 1.540 [8]\*\* | 42.15 ± 3.315 [8]\* | 34.94 ± 1.896 [8]\*\* | <.001 |
| **ABS CD4+ CD8-** | 31.16 ± 1.601 [8] | 27.71 ± 1.275 [8] | 27.19 ± 1.618 [8] | 25.36 ± 0.970 [8]\*\* | 27.39 ± 1.936 [8]\* | 22.23 ± 1.298 [8]\*\* | <.001 |
| **ABS CD4- CD8+** | 17.20 ± 0.859 [8] | 15.38 ± 0.785 [8] | 13.89 ± 1.009 [8]\* | 13.35 ± 0.732 [8]\*\* | 15.40 ± 0.969 [8]\* | 12.40 ± 0.769 [8]\*\* | 0.004 |
| **ABS CD4+ CD8+** | 0.19 ± 0.030 [8] | 0.15 ± 0.038 [8] | 0.09 ± 0.023 [8] | 0.15 ± 0.038 [8] | 0.16 ± 0.018 [8] | 0.09 ± 0.013 [8] | 0.133 |
| **ABS NK1.1+ CD3-** | 6.79 ± 0.285 [8] | 5.81 ± 0.249 [8] | 5.81 ± 0.239 [8] | 5.64 ± 0.287 [8]\* | 5.68 ± 0.469 [8] | 5.60 ± 0.392 [8]\* | 0.012 |
| **ABS Mac3+** | 7.70 ± 0.565 [8] | 6.71 ± 0.598 [8] | 6.10 ± 0.419 [8]\* | 5.31 ± 0.232 [8]\*\* | 5.83 ± 0.515 [8]\*\* | 4.68 ± 0.222 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **ABS Ig+** | 76.43 ± 4.696 [8] | 13.96 ± 1.919 [8]\*\* | <.001 |
| **ABS CD3+** | 48.73 ± 2.304 [8] | 27.05 ± 2.621 [8]\*\* | <.001 |
| **ABS CD4+ CD8-** | 31.16 ± 1.601 [8] | 14.96 ± 1.081 [8]\*\* | <.001 |
| **ABS CD4- CD8+** | 17.20 ± 0.859 [8] | 10.08 ± 0.800 [8]\*\* | <.001 |
| **ABS CD4+ CD8+** | 0.19 ± 0.030 [8] | 0.06 ± 0.018 [8]\*\* | 0.006 |
| **ABS Mac3+** | 7.70 ± 0.565 [8] | 2.13 ± 0.262 [8]\*\* | <.001 |

| **Parametera** | **Vehicle Control** | **AAGM1 1/10** | **Trendc** |
| --- | --- | --- | --- |
| **ABS NK1.1+ CD3-** | 6.79 ± 0.285 [8] | 1.40 ± 0.280 [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 DNA SYNTHESIS IN FEMALE MICE  STUDY 8** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Cells/ femur (X10^6)** | 1.29 ± 0.068 [8] | 0.95 ± 0.071 [8] | 0.79 ± 0.057 [8]\*\* | 1.04 ± 0.083 [8] | 1.14 ± 0.143 [8] | 1.02 ± 0.079 [8] | 0.386 |
| **DNA Synth. CPM (avg of 3 repl)** | 109712 ± 7669 [8] | 129404 ± 10416 [8] | 115094 ± 5331 [8] | 114859 ± 8294 [8] | 106487 ± 9711 [8] | 107040 ± 9008 [8] | 0.406 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Cells/ femur (X10^6)** | 1.29 ± 0.068 [8] | 0.59 ± 0.051 [8]\*\* | <.001 |
| **DNA Synth. CPM (avg of 3 repl)** | 109712 ± 7669 [8] | 137237 ± 7016 [8] | 0.074 |

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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 BODY WEIGHTS IN FEMALE MICE  STUDY 8** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 23.65 ± 0.295 [8] | 23.49 ± 0.349 [8] | 23.37 ± 0.331 [8] | 22.88 ± 0.348 [8] | 23.40 ± 0.420 [8] | 23.22 ± 0.447 [8] | 0.443 |
| **Body Weight Day 8 g** | 23.67 ± 0.522 [8] | 24.03 ± 0.565 [8] | 24.20 ± 0.455 [8] | 23.58 ± 0.576 [8] | 24.50 ± 0.379 [8] | 24.15 ± 0.519 [8] | 0.312 |
| **Body Weight Day 15 g** | 25.00 ± 0.490 [8] | 25.68 ± 0.580 [8] | 25.51 ± 0.710 [8] | 24.44 ± 0.795 [8] | 25.05 ± 0.592 [8] | 24.34 ± 0.631 [8] | 0.362 |
| **Body Weight Day 22 g** | 25.29 ± 0.649 [8] | 27.35 ± 0.793 [8] | 25.55 ± 0.573 [8] | 24.58 ± 0.847 [8] | 25.59 ± 0.610 [8] | 24.82 ± 0.753 [8] | 0.216 |
| **Body Weight Day 29 g** | 25.65 ± 0.749 [8] | 27.26 ± 0.787 [8] | 26.55 ± 0.854 [8] | 25.15 ± 0.903 [8] | 26.33 ± 0.520 [8] | 24.89 ± 0.724 [8] | 0.316 |
| **BW Day 8-1 g** | 0.02 ± 0.464 [8] | 0.53 ± 0.301 [8] | 0.83 ± 0.195 [8] | 0.70 ± 0.291 [8] | 1.10 ± 0.226 [8]\* | 0.93 ± 0.117 [8] | 0.045 |
| **BW Day 15-1 g** | 1.35 ± 0.438 [8] | 2.19 ± 0.331 [8] | 2.15 ± 0.432 [8] | 1.56 ± 0.474 [8] | 1.65 ± 0.292 [8] | 1.12 ± 0.379 [8] | 0.504 |
| **BW Day 22-1 g** | 1.65 ± 0.513 [8] | 3.85 ± 0.624 [8]\*\* | 2.18 ± 0.320 [8] | 1.70 ± 0.524 [8] | 2.19 ± 0.461 [8] | 1.60 ± 0.357 [8] | 0.213 |
| **BW Day 29-1 g** | 2.00 ± 0.594 [8] | 3.77 ± 0.581 [8] | 3.19 ± 0.567 [8] | 2.27 ± 0.640 [8] | 2.93 ± 0.348 [8] | 1.67 ± 0.454 [8] | 0.376 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 23.65 ± 0.295 [8] | 23.73 ± 0.386 [8] | 0.753 |
| **Body Weight Day 8 g** | 23.67 ± 0.522 [8] | 24.34 ± 0.517 [8] | 0.294 |
| **Body Weight Day 15 g** | 25.00 ± 0.490 [8] | 25.58 ± 0.489 [8] | 0.345 |
| **Body Weight Day 22 g** | 25.29 ± 0.649 [8] | 26.19 ± 0.599 [8] | 0.345 |
| **Body Weight Day 29 g** | 25.65 ± 0.749 [8] | 26.06 ± 0.512 [8] | 0.401 |
| **BW Day 8-1 g** | 0.02 ± 0.464 [8] | 0.61 ± 0.296 [8] | 0.294 |
| **BW Day 15-1 g** | 1.35 ± 0.438 [8] | 1.85 ± 0.189 [8] | 0.248 |
| **BW Day 22-1 g** | 1.65 ± 0.513 [8] | 2.46 ± 0.307 [8] | 0.103 |
| **BW Day 29-1 g** | 2.00 ± 0.594 [8] | 2.33 ± 0.238 [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 Williams’ test when a trend was present (P <0.01 from Jonckheere’s trend test), otherwise Dunnett’s 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 25 PFDA DNA SYNTHESIS IN FEMALE MICE  STUDY 9** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Cells/ femur (X10^6)** | 10.20 ± 0.661 [8] | 10.46 ± 0.968 [8] | 9.80 ± 0.494 [8] | 10.19 ± 0.701 [8] | 9.15 ± 0.751 [8] | 9.57 ± 0.827 [8] | 0.213 |
| **DNA Synth. CPM (avg of 3 repl)** | 86662 ± 6631 [8] | 82745 ± 4290 [8] | 76829 ± 4723 [8] | 90240 ± 7558 [8] | 84182 ± 1461 [8] | 73034 ± 3879 [8] | 0.427 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Cells/ femur (X10^6)** | 10.20 ± 0.661 [8] | 3.89 ± 0.567 [8]\*\* | 0.001 |
| **DNA Synth. CPM (avg of 3 repl)** | 86662 ± 6631 [8] | 63541 ± 4918 [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 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 MICE  STUDY 9** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parametera** | **Vehicle Control** | **0.3125 mg/kg** | **0.625 mg/kg** | **1.25 mg/kg** | **2.5 mg/kg** | **5.0 mg/kg** | **Trendb** |
| **Body Weight Day 1 g** | 22.01 ± 0.357 [8] | 22.27 ± 0.368 [8] | 22.02 ± 0.468 [8] | 22.05 ± 0.401 [8] | 21.80 ± 0.430 [8] | 21.79 ± 0.370 [8] | 0.504 |
| **Body Weight Day 8 g** | 22.76 ± 0.385 [8] | 22.39 ± 0.277 [8] | 22.49 ± 0.484 [8] | 22.37 ± 0.282 [8] | 21.97 ± 0.325 [8] | 22.89 ± 0.354 [8] | 0.857 |
| **Body Weight Day 15 g** | 23.85 ± 0.675 [8] | 23.42 ± 0.342 [8] | 23.03 ± 0.577 [8] | 23.10 ± 0.398 [8] | 22.69 ± 0.265 [8] | 23.44 ± 0.449 [8] | 0.312 |
| **Body Weight Day 22 g** | 24.57 ± 0.849 [8] | 23.43 ± 0.520 [8] | 23.81 ± 0.646 [8] | 23.41 ± 0.519 [8] | 23.41 ± 0.365 [8] | 23.67 ± 0.389 [8] | 0.718 |
| **Body Weight Day 29 g** | 25.43 ± 0.978 [8] | 24.50 ± 0.268 [8] | 24.37 ± 0.529 [8] | 24.40 ± 0.507 [8] | 24.00 ± 0.494 [8] | 23.89 ± 0.427 [8] | 0.190 |
| **BW Day 8-1 g** | 0.75 ± 0.158 [8] | 0.12 ± 0.290 [8] | 0.47 ± 0.333 [8] | 0.32 ± 0.283 [8] | 0.17 ± 0.348 [8] | 1.09 ± 0.121 [8] | 0.263 |
| **BW Day 15-1 g** | 1.84 ± 0.396 [8] | 1.15 ± 0.175 [8] | 1.01 ± 0.318 [8] | 1.05 ± 0.272 [8] | 0.89 ± 0.267 [8] | 1.65 ± 0.276 [8] | 0.678 |
| **BW Day 22-1 g** | 2.56 ± 0.606 [8] | 1.16 ± 0.306 [8]\* | 1.80 ± 0.269 [8] | 1.36 ± 0.302 [8] | 1.61 ± 0.289 [8] | 1.88 ± 0.306 [8] | 0.878 |
| **BW Day 29-1 g** | 3.42 ± 0.692 [8] | 2.23 ± 0.220 [8] | 2.35 ± 0.215 [8] | 2.35 ± 0.249 [8] | 2.20 ± 0.320 [8] | 2.10 ± 0.192 [8] | 0.178 |

| **Parametera** | **Vehicle Control** | **CPS 50 mg/kg** | **Trendc** |
| --- | --- | --- | --- |
| **Body Weight Day 1 g** | 22.01 ± 0.357 [8] | 21.93 ± 0.377 [8] | 0.674 |
| **Body Weight Day 8 g** | 22.76 ± 0.385 [8] | 22.44 ± 0.608 [8] | 0.674 |
| **Body Weight Day 15 g** | 23.85 ± 0.675 [8] | 22.92 ± 0.547 [8] | 0.345 |
| **Body Weight Day 22 g** | 24.57 ± 0.849 [8] | 23.55 ± 0.498 [8] | 0.462 |
| **Body Weight Day 29 g** | 25.43 ± 0.978 [8] | 23.09 ± 0.496 [8] | 0.189 |
| **BW Day 8-1 g** | 0.75 ± 0.158 [8] | 0.51 ± 0.460 [8] | 0.495 |
| **BW Day 15-1 g** | 1.84 ± 0.396 [8] | 0.99 ± 0.400 [8] | 0.093 |
| **BW Day 22-1 g** | 2.56 ± 0.606 [8] | 1.61 ± 0.278 [8] | 0.294 |
| **BW Day 29-1 g** | 3.42 ± 0.692 [8] | 1.15 ± 0.310 [8]\*\* | 0.016 |

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

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.

For the survival analysis on studies 6a-6c, a Cochran-Armitage test was used on the binary (0/1) survival data to get a single trend p-value for the study. Pairwise significance was determined using Fisher’s Exact Test.

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**

Armitage, P. (1971). Statistical Methods in Medical Research. John Wiley & Sons, Inc. pp. 362-365.

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.

Fisher, R.A. (1954). Statistical Methods for Research Workers. Oliver and Boyd. ISBN 0-05-002170-2.

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.