

NCTR PROTOCOL E0219001

**TWO YEAR CHRONIC TOXICOLOGY STUDY OF BISPHENOL A (BPA) [CAS # 80-05-7]
ADMINISTERED BY GAVAGE TO SPRAGUE-DAWLEY RATS (NCTR) FROM GESTATIONAL DAY 6
UNTIL BIRTH AND DIRECTLY TO F₁ PUPS FROM POSTNATAL DAY (PND) 1; CONTINUOUS AND
STOP DOSE (PND 21) EXPOSURES**

STATISTICAL REPORT

STATISTICAL ANALYSIS OF TERMINAL SACRIFICE BODY WEIGHT DATA

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Statistical Analysis of Terminal Sacrifice Body Weight Data

1. Objectives

1.1 Project Objectives

The goal of this two year chronic study is to characterize the long term toxicity of orally administered BPA, including developmental exposure, in the NCTR Sprague-Dawley (CD) rat over a broad dose range.

1.2 Analysis Objectives

The goal of this analysis is to evaluate the effects of exposure to BPA in Sprague-Dawley rats on two year body weight based on terminal sacrifice animals.

2. Experimental Design

The study design consisted of first generation female and male rats (F₀) for up to 600 mating pairs randomized to treatment groups in 5 litters. The goal of the F₀ matings was to obtain 352 study litters, 50 per dose group for vehicle controls and five BPA dose groups, 2.5, 25, 250, 2500, and 25000 µg/kg bw/day, and 26 for each of two EE₂ dose groups, 0.05 and 0.5 µg/kg bw/day. Dams were dosed daily from gestation day (GD) 6 until parturition. Dosing was by gavage for F₀ dams and F₁ pups, the second study generation. Litters were culled to 10 pups on PND 1. There were two study dosing arms of F₁ animals, daily continuous dosing to termination, and daily dose stopped at post-natal day (PND) 21. There was a vehicle control group and five BPA groups for each study dosing arm, and EE₂ daily dose groups for the continuous dosing arm only. From the F₁ litters, pups were allocated at weaning, PND 21, to the interim (1 year) and terminal (2 year) sacrifices for the core study. For vehicle and BPA terminal sacrifice groups, there were 50 pups each; for the interim sacrifice and the EE₂ terminal sacrifice groups, there were 20-26 pups each. Pups within litter and sex were assigned to different dosing arms and sacrifice times.

Body Weight Data

F₁ animals were weighed daily prior to dosing until weaning. After weaning, animals in the continuous dosing arm were weighed daily prior to dosing until PND 90±3. After PND 90±3, each animal was weighed weekly. For animals in the stop dose arm, body weights were recorded on weaning day and weekly thereafter.

3. Statistical Methods

Statistical analyses were performed separately for the BPA study arms, stop dose and continuous dose, and for EE₂ continuous dose. Body weight data collected from 4 to 104 weeks were analyzed using the last weekly observation for each animal, with PND 21 defined as the first day of week 4. Pairwise comparisons of means were performed using contrasts within a two-way repeated measures, mixed model analysis of variance (ANOVA) for females and males separately. Model terms were treatment group, weeks, and the interaction. Within-group correlations were modeled using a heterogeneous first-order autoregressive (ARH(1)) correlation structure, which allows for correlated differences in variability across time points. Tests of trend, increasing treatment effect with increasing dose, were performed for the BPA and vehicle control groups. Comparisons of treatment groups to control were performed with Dunnett's method for adjusted contrasts.

For analysis of each endpoint, a sensitivity analysis was also performed. During initial preweaning of animals, 263 core study terminal sacrifice animals (56 in vehicle control, 175 in BPA 2.5, 25, 250, 2500, and 25000 $\mu\text{g}/\text{kg}$ bw/day, and 32 in EE₂ $\mu\text{g}/\text{kg}$ bw/day dose groups) were held in the same rooms as a special BPA 250,000 $\mu\text{g}/\text{kg}$ bw/day high dose requested by an academic laboratory. In consultation with the Principal Investigator, to address the possibility of inadvertent exposure of the core study animals, a sensitivity analysis excluding these 263 animals was also performed to test the robustness of the results. Additional statistically significant pairwise comparisons from the sensitivity analysis are reported in the text.

Using all data collected for each animal, the observed post-weaning body weight was compared to the predicted body weight using a 5-point running median smoother and nearest neighbor interpolation. The threshold for outlier exclusion was a difference between the observed and predicted weights greater than 60 (g) for females and 65 (g) for males with graphical confirmation for week 4 due to rapid early post-weaning growth. Analysis was conducted on the remaining observed values after outlier exclusion.

4. Results

Results of analyses using all study animals are presented in Tables (Appendix A) and Figures (Appendix B). Outlier body weight data are listed in Tables (Appendix C).

4.1 BPA Treatments Stop Dose Arm

Summary statistics for BPA stop dose treatments are presented in Table 1 for females and in Table 2 for males.

The ANOVA omnibus test results are given in Table 3 for females and in Table 5 for males for the null hypothesis that all of the control and BPA stop dose treatment means for body weight are equal. The effect of week was significant for females and males (both $p < 0.001$).

Comparisons of least squares mean female body weights are presented in Table 4. There was a significant dose trend for the BPA stop dose group at week 4 ($p = 0.037$), although there were no significant differences for any dose compared to control. In the sensitivity analysis for the BPA stop dose treatments, there was an additional statistically significant difference compared to control for BPA stop dose 2500 $\mu\text{g}/\text{kg}$ bw/day at week 4, with relatively lower mean weight in the dosed group ($p = 0.016$, 12.1% lower than control).

Comparisons of least squares mean male body weights are presented in Table 6. There was a significant dose trend for the BPA stop dose group at week 4 ($p = 0.043$), although there were no significant differences for any dose compared to control. In the sensitivity analysis for BPA stop dose males, there were no additional significant results.

4.2 BPA Treatments Continuous Dose Arm

Summary statistics for BPA continuous dose treatments are presented in Table 7 for females and in Table 8 for males.

The ANOVA omnibus test results are given in Table 9 for females and in Table 11 for males for the null hypothesis that all of the control and BPA continuous dose treatment means for body weight are equal. The effect of week was significant for females and males (both $p < 0.001$).

Comparisons of least squares mean female body weights are presented in Table 10. There were significant differences compared to control for the BPA continuous dose 250 $\mu\text{g}/\text{kg}$ bw/day at

weeks 96, 100, and 104 ($p=0.049$, $=0.031$, and $=0.026$, respectively), with relatively higher means in the dosed group (10.7%, 12.4%, and 14.3% higher than control, respectively). In the sensitivity analysis for females, there was an additional statistically significant difference compared to control for BPA continuous dose 25000 $\mu\text{g}/\text{kg}$ bw/day at week 8 ($p=0.031$).

Comparisons of least squares mean male body weights are presented in Table 12. There were no statistically significant results for any BPA continuous dose group. In the sensitivity analysis for BPA continuous dose males, there were no additional significant results.

4.3 EE₂ Treatments Continuous Dose

Summary statistics for EE₂ continuous dose treatments are presented in Table 13 for females and in Table 14 for males.

The ANOVA omnibus test results are given in Table 15 for females and in Table 17 for males for the null hypothesis that all of the control and EE₂ continuous dose treatment means for body weight are equal. The effect of week was significant for females and males (both $p<0.001$), and the interaction term was significant for females ($p=0.034$).

Comparisons of least squares mean female body weights are presented in Table 16. There were significant differences compared to control for the EE₂ continuous dose 0.5 $\mu\text{g}/\text{kg}$ bw/day at weeks 4 and 8 ($p=0.019$ and $=0.002$, respectively). Means were relatively higher in the dosed group (6.2% and 8.0% higher than control, respectively).

Comparisons of least squares mean male body weights are presented in Table 18. There were no significant results for EE₂ continuous dose 0.05 $\mu\text{g}/\text{kg}$ bw/day or 0.5 $\mu\text{g}/\text{kg}$ bw/day at any week.

In the sensitivity analysis for the EE₂ continuous dose treatments, there were no additional statistically significant results for females or males.

5. Conclusions

5.1 BPA Treatments Stop Dose Arm

There was a statistically significant difference in the sensitivity analysis for females compared to control for BPA stop dose 2500 $\mu\text{g}/\text{kg}$ bw/day at week 4, with relatively lower means in the dosed group.

In the analyses for BPA stop dose males, there were no statistically significant results.

5.2 BPA Treatments Continuous Dose Arm

For females, there were significant differences for the BPA continuous dose 250 $\mu\text{g}/\text{kg}$ bw/day compared to control at weeks 96, 100, and 104, with relatively higher means in the dosed group. In the sensitivity analysis for females, there was an additional statistically significant difference compared to control for BPA continuous dose 25000 $\mu\text{g}/\text{kg}$ bw/day at week 8.

In the analyses for BPA continuous dose males, there were no statistically significant results.

5.3 EE₂ Treatments Continuous Dose

For females, there were significant differences compared to control for the EE₂ continuous dose 0.5 $\mu\text{g}/\text{kg}$ bw/day at weeks 4 and 8, with relatively higher means in the dosed group.

In the analyses for EE₂ continuous dose males, there were no statistically significant results.

Appendices

A. Statistical Tables

Analysis of Terminal Sacrifice Body Weight Data

a) BPA Treatments Stop Dose Arm

Table 1. Summary Statistics for Terminal Sacrifice Female Body Weight Bisphenol-A Stop-Dose Arm

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)																	
	0		2.5		25		250		2500		25000							
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
4	50	56.8	1.6	50	56.3	1.6	48	53.5	1.5	50	52.8	1.3	50	52.0	1.6	46	54.3	1.2
8	50	189.5	3.6	50	189.9	2.4	48	189.1	2.3	50	192.7	2.5	50	187.4	3.6	46	190.1	2.4
12	50	269.5	5.4	50	269.7	3.4	48	267.5	3.3	50	270.7	4.0	50	267.1	5.1	46	270.3	3.8
16	50	311.5	6.7	50	312.5	4.0	48	307.4	4.6	50	309.5	4.8	50	305.3	5.7	46	310.9	4.7
20	50	338.5	7.5	50	338.7	4.7	46	330.4	5.3	50	334.0	5.4	50	329.9	6.6	46	337.7	5.2
24	50	359.4	8.4	50	360.7	4.9	48	349.2	5.9	50	352.7	6.2	49	350.4	6.9	46	357.6	5.7
28	50	378.6	9.5	50	375.4	5.6	48	364.6	6.6	50	369.9	7.0	49	365.8	7.7	46	376.1	6.3
32	50	393.1	10.3	48	393.2	6.3	48	380.2	7.3	50	383.6	7.7	49	380.8	8.3	46	392.4	6.9
36	50	409.4	10.5	50	409.3	7.1	48	396.7	7.9	50	403.3	8.6	49	394.2	9.1	46	408.8	7.7
40	43	420.3	11.1	47	427.6	7.8	44	414.1	8.8	44	417.6	10.0	47	411.2	9.9	44	426.9	8.6
44	47	436.4	11.0	50	445.8	8.7	48	425.9	9.2	50	434.8	9.5	48	425.6	10.2	46	444.8	9.2
48	49	457.1	11.6	50	465.5	9.5	48	445.8	9.5	50	451.3	10.2	49	443.6	10.9	46	462.6	10.0
52	49	479.4	12.2	49	488.7	10.3	47	462.1	10.2	50	473.5	10.9	49	458.9	11.4	46	477.3	10.6
56	49	496.9	12.8	49	505.9	10.4	47	482.5	11.0	50	496.2	11.6	49	480.3	12.1	45	495.2	11.9
60	48	516.0	13.6	46	524.3	11.4	47	502.1	11.4	50	515.2	11.9	48	495.8	12.4	44	512.9	13.5
64	48	536.4	14.7	45	549.2	12.7	47	520.5	12.1	50	537.2	12.4	48	516.7	13.2	43	533.4	15.2
68	47	557.5	15.9	44	572.9	13.4	43	539.9	13.1	46	546.3	13.0	47	536.6	13.8	39	550.5	15.3
72	44	570.6	18.0	39	579.6	12.9	41	551.7	14.5	44	560.6	14.2	45	555.5	15.6	35	551.6	14.2
76	36	569.7	18.6	40	598.1	13.5	39	568.5	14.9	41	573.6	15.4	41	568.1	16.3	35	574.7	15.5
80	34	575.8	18.2	39	619.2	14.9	35	574.7	14.7	36	585.6	18.3	38	579.5	17.4	35	589.2	15.8
84	31	588.5	21.1	32	633.4	18.4	30	601.3	17.8	34	605.1	18.6	36	591.4	18.7	31	604.2	19.3
88	28	594.6	22.3	26	623.7	19.5	26	599.4	17.8	31	614.2	21.5	33	605.5	21.0	29	613.0	20.1
92	23	590.8	28.1	20	626.4	22.7	20	590.4	20.6	28	626.2	23.9	31	609.0	23.6	26	625.2	21.5
96	20	599.9	33.2	16	607.5	20.0	16	594.9	25.4	23	651.1	29.2	24	633.0	28.0	22	616.1	23.6
100	17	600.2	29.9	16	624.6	21.0	15	613.6	27.5	18	650.4	37.0	19	613.8	34.1	17	609.9	29.1
104	11	607.6	44.9	13	630.6	23.1	13	595.0	25.4	13	629.6	39.0	17	641.4	34.9	13	623.3	35.1

Analysis of Terminal Sacrifice Body Weight Data

Table 2. Summary Statistics for Terminal Sacrifice Male Body Weight Bisphenol-A Stop-Dose Arm

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}^{\text{0.75}}/\text{day}$)																	
	0		2.5		25		250		2500		25000							
N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
4	50	61.0	1.6	48	60.3	2.1	48	58.7	1.7	50	56.4	1.5	50	57.7	1.9	46	57.2	1.6
8	49	270.5	3.8	48	272.8	4.6	48	281.4	3.9	50	279.4	4.2	50	271.0	4.4	46	268.5	4.6
12	49	427.6	5.1	48	425.0	5.9	48	436.6	6.3	50	433.0	5.4	50	426.3	5.5	46	428.2	6.7
16	49	508.6	6.1	48	507.9	7.3	48	522.3	8.0	50	515.4	6.8	50	510.9	6.1	46	515.0	7.5
20	49	567.3	6.5	48	564.3	7.9	48	581.6	9.5	50	571.8	7.7	50	569.3	6.7	43	573.6	9.1
24	49	606.4	7.2	48	601.9	9.1	48	619.0	10.5	50	612.7	8.7	49	608.5	7.5	45	612.4	9.8
28	48	637.3	8.4	48	630.5	9.5	45	648.2	11.3	50	641.9	9.8	49	635.1	8.2	45	638.6	10.2
32	47	664.3	9.1	48	654.6	10.0	48	673.4	11.9	50	665.4	10.4	49	660.6	8.8	45	664.4	11.1
36	49	687.9	9.6	48	681.0	11.3	48	698.0	12.4	50	687.4	11.3	49	683.1	9.3	45	688.3	11.9
40	47	704.2	9.7	44	695.4	11.4	44	723.7	13.8	44	705.1	14.0	46	700.0	9.7	42	710.5	14.1
44	46	731.6	11.7	48	724.3	12.5	47	746.2	13.8	50	730.7	13.5	48	722.9	10.5	43	732.2	14.8
48	49	751.5	12.0	48	745.4	13.3	48	762.6	14.9	50	748.8	14.9	49	744.3	11.2	43	755.1	15.9
52	49	771.7	12.8	47	763.1	14.1	48	780.6	15.4	49	756.9	14.2	49	756.5	11.5	43	770.4	16.7
56	49	788.6	14.0	47	777.6	14.9	48	800.5	16.1	49	773.4	14.6	49	778.5	12.7	42	792.5	18.1
60	48	811.3	15.0	46	798.7	16.6	46	812.8	17.0	46	797.5	15.7	49	793.4	14.0	42	810.5	19.2
64	48	830.6	15.7	44	815.4	16.5	46	831.6	18.0	45	816.5	17.3	47	814.9	14.8	42	825.6	20.1
68	46	855.1	16.4	43	834.2	18.2	46	845.9	19.4	45	836.6	17.4	45	835.7	16.3	39	848.5	22.2
72	46	873.7	17.1	42	850.6	19.1	43	861.4	21.9	42	837.1	19.1	44	858.4	18.5	35	865.6	21.9
76	44	883.8	17.3	39	870.0	21.2	40	895.5	22.5	37	873.8	19.4	41	868.6	18.4	34	878.3	24.1
80	43	887.8	17.8	39	883.4	23.1	38	912.9	24.8	33	891.5	22.1	40	875.0	20.4	29	892.8	29.5
84	39	896.4	16.8	35	873.0	21.5	36	919.6	25.1	30	894.9	23.7	37	879.0	18.5	26	914.9	32.4
88	37	906.0	17.8	31	884.7	25.8	33	932.0	22.9	26	907.6	30.2	34	874.3	20.7	23	918.0	34.2
92	32	902.7	16.3	27	878.6	25.4	31	910.8	22.3	21	935.1	34.8	30	887.0	23.0	20	955.1	28.0
96	29	903.4	19.1	25	874.1	28.0	27	900.8	26.0	17	941.0	44.1	27	883.6	27.0	16	924.7	29.8
100	21	928.0	19.8	18	876.1	29.1	21	892.9	30.3	13	953.2	48.8	25	877.5	26.2	14	931.7	30.7
104	16	907.6	22.8	16	845.1	29.7	16	907.5	32.8	13	941.3	44.7	16	863.2	33.1	10	893.5	37.0

Analysis of Terminal Sacrifice Body Weight Data

*Table 3. ANOVA Results for Body Weight Terminal Sacrifice
Female Bisphenol-A Stop-Dose Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)*

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	5	288	1.249	0.286
Week	25	5968	1859.714	<.001
Dose*Week	125	5968	0.351	1.000

Analysis of Terminal Sacrifice Body Weight Data

Table 4. Comparisons of Least Squares Means for Body Weight Terminal Sacrifice Female Bisphenol-A Stop-Dose Arm¹

Week	Dose ($\mu\text{g}/\text{kg}/\text{bw}/\text{day}$)																							
	0				2.5				25				250				2500				25000			
	Mean	SE	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	
4	56.7	1.5	0.037	56.3	1.5	99.3	1.000	53.6	1.5	94.4	0.402	52.8	1.5	93.1	0.206	52.0	1.5	91.7	0.089	54.3	1.5	95.7	0.666	
8	189.5	2.9	0.958	189.9	2.9	100.2	1.000	189.1	2.9	99.8	1.000	192.6	2.9	101.6	0.907	187.4	2.9	98.9	0.981	190.0	3.0	100.3	1.000	
12	269.5	4.2	0.988	269.7	4.2	100.1	1.000	267.6	4.3	99.3	0.998	270.7	4.2	100.4	1.000	267.2	4.2	99.2	0.995	270.3	4.4	100.3	1.000	
16	311.4	5.1	0.605	312.5	5.1	100.4	1.000	307.5	5.2	98.7	0.977	309.3	5.1	99.3	0.999	305.4	5.1	98.1	0.874	310.8	5.3	99.8	1.000	
20	338.4	5.8	0.582	338.8	5.8	100.1	1.000	331.1	5.9	97.9	0.853	333.8	5.8	98.7	0.974	329.9	5.8	97.5	0.759	337.7	6.1	99.8	1.000	
24	359.2	6.4	0.430	360.7	6.4	100.4	1.000	349.3	6.5	97.2	0.711	352.5	6.4	98.1	0.915	348.2	6.4	96.9	0.617	357.5	6.7	99.5	1.000	
28	378.4	7.2	0.485	375.4	7.2	99.2	0.998	364.7	7.3	96.4	0.527	369.7	7.2	97.7	0.858	363.5	7.2	96.1	0.442	376.0	7.5	99.4	1.000	
32	392.9	7.8	0.552	391.9	7.8	99.8	1.000	380.4	7.9	96.8	0.687	383.4	7.8	97.6	0.859	378.6	7.9	96.4	0.567	392.4	8.2	99.9	1.000	
36	409.2	8.5	0.510	409.1	8.4	100.0	1.000	396.8	8.6	97.0	0.757	403.0	8.5	98.5	0.981	392.1	8.5	95.8	0.472	408.7	8.8	99.9	1.000	
40	425.4	9.1	0.557	427.8	9.0	100.6	1.000	409.9	9.2	96.3	0.626	418.9	9.0	98.5	0.981	406.9	9.1	95.6	0.455	427.2	9.4	100.4	1.000	
44	442.5	9.5	0.557	446.0	9.5	100.8	0.999	424.8	9.7	96.0	0.556	435.2	9.5	98.4	0.976	422.3	9.6	95.4	0.426	445.1	10.0	100.6	1.000	
48	461.3	10.1	0.507	465.6	10.1	100.9	0.998	444.8	10.3	96.4	0.674	451.7	10.1	97.9	0.944	441.5	10.3	95.7	0.503	462.9	10.6	100.4	1.000	
52	483.3	10.7	0.233	487.8	10.7	100.9	0.999	461.9	10.9	95.6	0.489	473.9	10.7	98.1	0.958	457.0	10.9	94.6	0.286	477.6	11.2	98.8	0.996	
56	500.6	11.4	0.388	505.1	11.4	100.9	0.999	482.2	11.7	96.3	0.685	496.5	11.4	99.2	0.999	478.4	11.5	95.6	0.511	497.0	12.0	99.3	1.000	
60	520.3	12.1	0.372	525.5	12.2	101.0	0.998	501.8	12.3	96.4	0.726	515.5	12.0	99.1	0.999	497.3	12.2	95.6	0.533	516.0	12.7	99.2	0.999	
64	540.6	13.0	0.328	549.3	13.2	101.6	0.987	520.1	13.2	96.2	0.703	537.5	12.9	99.4	1.000	518.2	13.1	95.9	0.622	534.0	13.7	98.8	0.997	
68	562.2	13.1	0.245	574.9	13.4	102.3	0.942	539.5	13.5	96.0	0.627	554.5	13.1	98.6	0.992	540.1	13.2	96.1	0.642	553.9	13.9	98.5	0.991	
72	577.9	13.9	0.289	589.3	14.3	102.0	0.971	552.4	14.2	95.6	0.570	572.2	13.9	99.0	0.999	555.9	14.0	96.2	0.691	568.6	14.9	98.4	0.989	
76	590.2	14.5	0.464	609.3	14.5	103.2	0.818	567.4	14.7	96.1	0.701	584.3	14.2	99.0	0.999	574.1	14.3	97.3	0.894	589.9	15.2	100.0	1.000	
80	606.3	15.3	0.409	628.9	15.1	103.7	0.741	583.2	15.4	96.2	0.727	599.0	15.0	98.8	0.997	593.0	15.0	97.8	0.958	603.4	15.8	99.5	1.000	
84	619.8	16.9	0.412	647.3	16.7	104.4	0.663	604.0	17.1	97.4	0.947	614.9	16.6	99.2	1.000	605.5	16.5	97.7	0.963	619.3	17.5	99.9	1.000	
88	628.9	18.2	0.568	658.0	18.3	104.6	0.687	619.7	18.6	98.5	0.997	630.1	17.7	100.2	1.000	621.2	17.5	98.8	0.998	631.5	18.4	100.4	1.000	
92	632.4	20.7	0.761	667.3	21.1	105.5	0.647	629.8	21.4	99.6	1.000	639.8	19.8	101.2	0.999	630.3	19.4	99.7	1.000	642.2	20.6	101.5	0.997	
96	633.2	22.7	0.881	679.4	23.9	107.3	0.487	639.9	24.1	101.1	1.000	654.5	21.6	103.4	0.940	638.3	21.2	100.8	1.000	649.3	22.3	102.5	0.982	
100	638.9	25.2	0.661	691.5	26.2	108.2	0.454	651.1	26.7	101.9	0.997	669.2	24.1	104.7	0.854	635.7	23.5	99.5	1.000	650.5	24.8	101.8	0.998	
104	643.5	28.8	0.637	695.2	28.9	108.0	0.583	651.9	29.2	101.3	1.000	679.9	27.2	105.7	0.825	641.7	25.7	99.7	1.000	647.8	27.8	100.7	1.000	

¹ All p-values and % are relative to the 0 dose control group, except p-value for trend shown below control.

Analysis of Terminal Sacrifice Body Weight Data

*Table 5. ANOVA Results for Body Weight Terminal Sacrifice
Male Bisphenol-A Stop-Dose Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)*

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	5	286	0.519	0.762
Week	25	5976	2203.306	<.001
Dose*Week	125	5976	0.497	0.999

Analysis of Terminal Sacrifice Body Weight Data

Table 6. Comparisons of Least Squares Means for Body Weight Terminal Sacrifice Male Bisphenol-A Stop-Dose Arm¹

Week	Dose ($\mu\text{g}/\text{kg}/\text{bw}/\text{day}$)																						
	0				2.5				25				250				2500				25000		
	Mean	SE	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value
4	61.0	1.7	0.043	60.3	1.7	98.9	0.999	58.8	1.7	96.4	0.829	56.4	1.7	92.6	0.213	57.7	1.7	94.6	0.514	57.1	1.8	93.7	0.380
8	271.1	4.2	0.564	272.8	4.3	100.6	0.999	281.6	4.3	103.9	0.264	279.5	4.2	103.1	0.473	271.0	4.2	100.0	1.000	268.5	4.4	99.0	0.991
12	428.4	5.7	0.988	425.0	5.8	99.2	0.993	436.9	5.8	102.0	0.743	433.0	5.7	101.1	0.969	426.3	5.7	99.5	0.999	428.2	6.0	100.0	1.000
16	509.4	6.9	0.618	507.9	7.0	99.7	1.000	522.7	7.0	102.6	0.526	515.4	6.9	101.2	0.961	510.9	6.9	100.3	1.000	514.9	7.2	101.1	0.974
20	568.2	7.8	0.673	564.3	7.9	99.3	0.997	582.1	7.9	102.5	0.595	571.8	7.8	100.6	0.998	569.3	7.8	100.2	1.000	572.9	8.1	100.8	0.993
24	607.3	8.7	0.625	601.8	8.8	99.1	0.990	619.6	8.8	102.0	0.779	612.7	8.7	100.9	0.991	608.6	8.7	100.2	1.000	611.8	9.0	100.7	0.996
28	636.8	9.5	0.871	630.5	9.6	99.0	0.987	648.8	9.6	101.9	0.846	641.9	9.4	100.8	0.995	635.3	9.4	99.8	1.000	638.0	9.8	100.2	1.000
32	664.3	10.1	0.913	654.5	10.2	98.5	0.939	672.3	10.1	101.2	0.974	665.4	10.0	100.2	1.000	660.7	10.1	99.5	0.999	663.8	10.4	99.9	1.000
36	688.3	10.8	0.951	680.9	11.0	98.9	0.986	697.0	10.9	101.3	0.971	687.4	10.8	99.9	1.000	683.2	10.9	99.3	0.998	687.7	11.3	99.9	1.000
40	709.4	11.7	0.979	702.5	12.0	99.0	0.993	721.5	11.9	101.7	0.925	710.0	11.8	100.1	1.000	700.8	11.8	98.8	0.980	712.2	12.3	100.4	1.000
44	729.6	12.5	0.933	724.0	12.7	99.2	0.998	741.8	12.6	101.7	0.937	731.2	12.3	100.2	1.000	723.8	12.5	99.2	0.998	733.7	13.1	100.6	1.000
48	751.4	13.3	0.930	745.2	13.6	99.2	0.998	761.8	13.5	101.4	0.976	749.5	13.3	99.7	1.000	744.5	13.4	99.1	0.996	756.3	14.2	100.7	0.999
52	771.6	13.7	0.806	761.4	14.0	98.7	0.980	780.0	13.9	101.1	0.992	765.4	13.7	99.2	0.998	756.7	13.8	98.1	0.908	771.5	14.6	100.0	1.000
56	788.8	14.6	0.972	776.3	15.0	98.4	0.965	800.4	14.8	101.5	0.972	782.1	14.6	99.2	0.998	778.8	14.7	98.7	0.986	791.8	15.6	100.4	1.000
60	809.4	15.6	0.878	796.7	16.0	98.4	0.970	815.1	15.8	100.7	0.999	801.1	15.7	99.0	0.995	793.8	15.7	98.1	0.930	809.8	16.7	100.0	1.000
64	828.8	16.4	0.825	809.7	16.9	97.7	0.886	834.3	16.7	100.7	1.000	816.6	16.6	98.5	0.980	811.6	16.5	97.9	0.918	825.0	17.6	99.5	1.000
68	847.3	17.4	0.860	826.3	18.0	97.5	0.871	849.1	17.6	100.2	1.000	831.3	17.5	98.1	0.950	830.9	17.6	98.1	0.946	842.8	18.7	99.5	1.000
72	866.5	18.0	0.789	838.3	18.7	96.7	0.716	863.0	18.4	99.6	1.000	839.5	18.4	96.9	0.743	850.5	18.3	98.2	0.958	855.4	19.7	98.7	0.993
76	874.6	18.5	0.906	852.5	19.3	97.5	0.878	882.7	19.0	100.9	0.998	858.2	19.2	98.1	0.959	861.2	18.9	98.5	0.982	870.5	20.4	99.5	1.000
80	883.0	19.6	0.842	867.4	20.6	98.2	0.975	896.7	20.3	101.6	0.985	877.0	20.8	99.3	1.000	866.6	20.1	98.2	0.968	880.4	22.2	99.7	1.000
84	892.9	19.5	0.829	870.7	20.4	97.5	0.897	899.7	20.2	100.8	0.999	881.0	21.0	98.7	0.993	872.8	20.0	97.7	0.925	887.9	22.4	99.4	1.000
88	899.8	19.9	0.723	877.7	21.1	97.5	0.909	903.7	20.8	100.4	1.000	892.1	22.1	99.1	0.999	870.1	20.6	96.7	0.749	893.9	23.5	99.3	1.000
92	891.5	19.9	0.823	880.7	21.1	98.8	0.996	892.5	20.6	100.1	1.000	898.5	22.6	100.8	1.000	873.7	20.5	98.0	0.957	902.6	23.8	101.2	0.996
96	884.1	21.7	0.693	878.4	23.4	99.4	1.000	880.1	22.6	99.5	1.000	900.5	26.1	101.9	0.985	869.5	22.6	98.3	0.988	901.3	27.0	101.9	0.984
100	900.4	22.7	0.998	865.8	24.0	96.2	0.741	865.4	23.1	96.1	0.719	905.4	27.3	100.6	1.000	853.4	22.5	94.8	0.440	899.7	27.8	99.9	1.000
104	899.7	24.4	0.584	851.3	25.6	94.6	0.510	849.2	24.9	94.4	0.455	898.7	28.9	99.9	1.000	830.6	24.5	92.3	0.169	877.5	30.4	97.5	0.971

¹ All p-values and % are relative to the 0 dose control group, except p-value for trend shown below control.

Analysis of Terminal Sacrifice Body Weight Data

b) BPA Treatments Continuous Dose Arm

Table 7. Summary Statistics for Terminal Sacrifice Female Body Weight Bisphenol-A Continuous Dose Arm

		Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)																	
		0			2.5			25			250			2500			25000		
Week	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
4	50	75.4	0.9	48	76.2	1.0	46	77.5	1.1	49	75.7	0.9	50	74.2	1.2	46	75.5	1.0	
8	50	196.0	2.6	48	201.2	2.7	46	202.5	2.4	49	198.7	2.0	50	197.5	2.7	45	203.8	2.6	
12	50	266.1	3.9	48	269.3	4.3	46	270.2	3.8	49	266.9	2.7	50	265.8	3.8	45	269.3	3.2	
16	50	302.5	5.0	47	305.1	5.0	46	303.4	5.0	49	298.9	3.2	50	299.8	4.2	45	301.9	3.9	
20	50	324.4	5.7	47	327.1	5.9	46	325.4	5.6	49	319.1	3.9	50	319.4	4.9	45	320.8	4.4	
24	50	342.3	6.3	46	344.8	6.6	45	345.5	6.5	49	336.5	4.6	50	336.0	5.3	45	338.5	5.2	
28	50	358.8	6.8	46	360.3	7.3	45	362.0	7.2	49	353.5	5.0	50	352.0	6.0	45	355.6	5.4	
32	50	372.4	7.6	46	375.8	8.1	45	376.4	7.9	49	366.3	5.5	50	365.5	6.3	45	368.7	5.9	
36	50	387.2	8.1	46	391.6	9.0	45	392.6	8.5	49	384.1	6.4	50	375.3	6.6	45	379.3	6.2	
40	50	401.7	8.8	46	406.8	10.2	45	406.9	9.6	48	396.4	7.0	49	387.8	7.6	45	394.2	7.0	
44	50	417.3	9.5	45	420.9	11.0	45	419.0	10.5	47	410.5	7.5	48	402.8	7.6	45	409.6	7.6	
48	50	430.9	9.9	44	438.5	12.1	44	437.0	11.5	48	426.1	7.9	48	419.0	8.5	45	423.5	8.1	
52	50	447.2	10.5	44	456.5	13.1	44	451.1	12.4	48	447.6	8.4	48	434.4	8.9	45	442.2	8.6	
56	50	463.0	11.2	44	473.6	14.2	44	462.7	13.3	47	465.9	8.9	48	449.2	9.8	45	456.8	9.3	
60	50	478.4	11.6	44	492.4	14.9	43	483.6	13.9	47	486.8	9.5	48	467.6	10.7	45	474.1	9.8	
64	49	495.1	12.0	44	509.6	15.6	42	501.7	15.2	47	504.1	10.4	44	476.7	10.9	45	491.3	10.5	
68	47	506.4	12.3	44	531.7	16.8	41	519.3	16.5	46	527.5	11.1	39	489.1	12.8	44	505.8	10.7	
72	44	519.7	13.5	43	543.9	17.6	38	544.3	17.9	44	546.7	11.3	36	497.0	12.5	42	520.5	11.6	
76	40	530.9	15.5	39	549.3	19.4	34	563.8	20.7	41	564.0	13.3	33	499.9	11.7	38	522.4	11.7	
80	39	542.5	16.4	34	562.5	22.3	26	560.5	18.6	40	571.1	13.2	31	513.9	13.2	33	536.6	12.5	
84	35	533.0	15.0	33	576.9	23.7	26	573.9	19.6	38	579.1	14.8	27	521.0	14.2	29	541.9	13.9	
88	32	534.0	17.5	31	583.8	26.3	24	585.0	22.3	27	587.7	19.6	24	526.6	17.4	28	556.4	14.8	
92	26	530.1	15.3	26	584.5	21.6	18	565.3	20.8	22	608.4	23.4	21	525.7	19.0	27	564.5	16.4	
96	23	531.3	16.8	22	603.8	23.4	16	594.5	20.2	19	615.7	25.1	18	540.4	23.0	21	569.1	18.7	
100	17	536.6	20.6	21	621.4	25.7	14	593.5	15.9	16	634.3	32.2	13	528.1	17.0	17	584.1	18.3	
104	17	534.1	22.3	18	618.7	28.1	13	607.1	17.8	12	622.0	35.8	11	524.2	22.0	9	597.3	33.8	

Analysis of Terminal Sacrifice Body Weight Data

Table 8. Summary Statistics for Terminal Sacrifice Male Body Weight Bisphenol-A Continuous Dose Arm

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}^{\text{day}}$)																	
	0		2.5		25		250		2500		25000							
N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
4	50	83.9	1.2	48	84.0	1.0	48	85.7	1.1	50	83.9	1.2	50	81.5	1.2	46	85.4	1.3
8	50	294.9	3.9	48	301.7	4.0	48	297.0	3.9	50	290.5	4.0	50	292.5	4.0	46	304.6	3.8
12	49	428.8	7.0	47	434.1	5.1	48	424.9	5.3	50	418.7	5.1	50	420.1	5.3	46	435.4	5.0
16	49	503.0	9.5	47	505.9	5.9	48	495.9	6.4	50	492.1	5.7	50	495.8	6.5	46	505.1	6.0
20	49	550.3	11.3	45	554.5	7.0	48	546.0	7.6	50	542.6	6.0	50	542.8	7.2	46	552.4	6.5
24	49	585.9	12.1	47	590.6	7.4	48	583.4	8.5	50	580.7	6.6	50	576.9	8.1	46	586.5	7.1
28	49	614.2	14.2	46	620.3	8.2	48	609.2	8.7	50	612.1	7.2	50	603.2	8.6	46	614.0	7.6
32	49	639.2	15.9	46	643.2	8.9	48	631.4	9.6	50	640.6	7.7	50	625.3	9.0	46	637.4	8.0
36	48	646.9	10.1	46	663.4	9.7	47	653.8	10.4	50	660.7	8.8	50	643.0	9.2	46	656.4	8.9
40	48	666.8	10.5	46	685.2	10.2	48	671.9	11.1	49	682.3	9.8	50	660.2	9.3	46	674.3	9.3
44	47	684.1	11.4	45	699.8	10.1	47	690.8	11.6	49	703.2	10.8	49	678.2	9.9	46	687.4	9.9
48	47	700.5	11.8	45	716.6	11.0	47	706.7	12.8	48	729.1	10.8	49	696.1	10.3	44	706.6	10.5
52	47	718.6	12.7	45	732.4	11.6	44	719.1	12.4	47	745.6	10.1	48	712.1	11.1	43	727.4	11.4
56	47	735.5	13.0	45	749.9	12.6	46	744.6	14.2	46	765.1	11.0	47	726.4	11.9	41	749.8	12.2
60	47	748.5	13.4	45	767.9	13.3	45	756.4	16.3	45	783.6	12.0	46	743.4	12.5	40	769.7	13.3
64	46	765.2	13.9	44	790.8	14.1	44	779.1	17.1	45	802.6	12.6	46	755.1	13.6	40	790.9	14.2
68	45	783.3	15.1	42	805.3	14.1	44	800.0	18.6	43	818.2	13.9	43	783.7	14.9	37	814.6	16.0
72	42	792.5	16.7	41	821.3	14.7	40	822.5	19.7	40	838.0	14.6	42	798.9	16.2	37	832.1	17.3
76	41	801.1	18.8	40	839.8	15.8	39	841.9	20.4	39	858.1	15.1	40	817.3	16.8	34	847.6	19.1
80	38	818.9	19.1	38	857.5	17.8	36	846.1	21.8	39	868.1	17.2	37	827.5	17.3	31	862.3	19.5
84	34	826.6	20.9	37	867.2	18.7	29	858.5	25.4	36	890.2	18.6	33	833.1	15.8	29	875.3	20.8
88	30	826.3	23.4	35	865.3	18.9	27	866.6	25.2	31	893.5	20.0	30	829.3	17.7	25	871.1	21.4
92	26	822.6	27.1	31	857.8	22.5	25	872.8	25.7	24	904.8	23.9	27	819.0	17.4	24	867.5	21.7
96	23	831.2	29.8	25	864.3	24.3	22	883.4	22.8	24	913.9	24.2	24	834.4	18.9	16	860.4	27.4
100	20	822.7	36.5	21	854.0	26.5	19	856.1	24.8	22	903.8	29.4	20	845.9	21.8	14	894.2	23.3
104	18	817.6	40.1	16	876.6	25.1	17	846.6	29.7	14	945.7	35.5	16	842.0	21.6	12	863.6	11.7

Analysis of Terminal Sacrifice Body Weight Data

*Table 9. ANOVA Results for Body Weight Terminal Sacrifice
Female Bisphenol-A Continuous Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)*

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	5	283	1.642	0.148
Week	25	5814	1643.424	<.001
Dose*Week	125	5814	0.527	0.999

Analysis of Terminal Sacrifice Body Weight Data

Table 10. Comparisons of Least Squares Means for Body Weight Terminal Sacrifice Female Bisphenol-A Continuous Dose Arm¹

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{bw}/\text{day}$)																						
	0				2.5				25				250				2500				25000		
	Mean	SE	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value
4	75.4	1.0	0.390	76.2	1.0	101.0	0.978	77.5	1.0	102.8	0.432	75.7	1.0	100.4	1.000	74.2	1.0	98.5	0.877	75.5	1.0	100.1	1.000
8	196.0	2.5	0.211	201.2	2.5	102.7	0.426	202.5	2.6	103.3	0.239	198.7	2.5	101.4	0.902	197.5	2.5	100.8	0.990	204.2	2.6	104.2	0.084
12	266.1	3.6	0.875	269.3	3.6	101.2	0.957	270.2	3.7	101.5	0.897	266.9	3.6	100.3	1.000	265.8	3.6	99.9	1.000	269.9	3.7	101.4	0.924
16	302.5	4.3	0.657	303.7	4.4	100.4	1.000	303.4	4.5	100.3	1.000	298.9	4.4	98.8	0.964	299.8	4.3	99.1	0.989	302.5	4.5	100.0	1.000
20	324.4	5.0	0.356	325.6	5.1	100.4	1.000	325.4	5.2	100.3	1.000	319.1	5.1	98.4	0.919	319.4	5.0	98.5	0.935	321.4	5.3	99.1	0.993
24	342.3	5.6	0.348	343.3	5.8	100.3	1.000	344.4	5.9	100.6	0.999	336.5	5.7	98.3	0.922	336.0	5.6	98.2	0.896	339.2	5.9	99.1	0.995
28	358.8	6.2	0.440	358.8	6.4	100.0	1.000	360.9	6.5	100.6	0.999	353.5	6.2	98.5	0.964	352.0	6.2	98.1	0.903	356.2	6.5	99.3	0.999
32	372.4	6.8	0.385	374.3	7.0	100.5	1.000	375.4	7.1	100.8	0.998	366.3	6.8	98.4	0.955	365.5	6.8	98.2	0.928	369.4	7.1	99.2	0.998
36	387.2	7.3	0.159	390.2	7.6	100.8	0.999	391.6	7.7	101.1	0.993	384.1	7.4	99.2	0.999	375.3	7.3	96.9	0.673	379.9	7.7	98.1	0.939
40	401.7	8.2	0.178	405.3	8.5	100.9	0.998	405.8	8.6	101.0	0.997	397.4	8.3	98.9	0.996	388.1	8.2	96.6	0.651	394.8	8.6	98.3	0.969
44	417.3	8.7	0.206	418.1	9.0	100.2	1.000	418.0	9.1	100.2	1.000	411.3	8.8	98.6	0.986	400.7	8.7	96.0	0.525	410.2	9.2	98.3	0.972
48	430.9	9.4	0.203	437.2	9.8	101.5	0.988	434.5	9.9	100.8	0.999	427.0	9.5	99.1	0.998	416.9	9.5	96.8	0.740	424.1	9.9	98.4	0.983
52	447.2	10.0	0.289	455.2	10.5	101.8	0.975	448.7	10.6	100.3	1.000	448.5	10.1	100.3	1.000	432.4	10.1	96.7	0.746	442.7	10.5	99.0	0.998
56	463.0	10.8	0.287	472.4	11.3	102.0	0.964	460.4	11.4	99.4	1.000	465.8	10.9	100.6	1.000	447.2	10.9	96.6	0.753	457.3	11.4	98.8	0.996
60	478.4	11.3	0.375	491.3	12.0	102.7	0.900	477.6	12.0	99.8	1.000	486.7	11.5	101.7	0.981	465.7	11.5	97.3	0.897	474.6	11.9	99.2	1.000
64	494.6	11.9	0.391	508.5	12.6	102.8	0.892	495.1	12.7	100.1	1.000	503.9	12.2	101.9	0.975	480.8	12.2	97.2	0.886	491.8	12.5	99.4	1.000
68	509.7	12.7	0.483	530.6	13.3	104.1	0.679	508.9	13.5	99.8	1.000	524.9	12.9	103.0	0.870	499.9	13.2	98.1	0.977	509.6	13.3	100.0	1.000
72	524.1	13.2	0.452	543.6	13.8	103.7	0.759	527.5	14.1	100.6	1.000	542.1	13.4	103.4	0.800	512.6	13.9	97.8	0.964	522.6	13.8	99.7	1.000
76	537.7	14.2	0.337	558.8	14.7	103.9	0.751	545.7	15.2	101.5	0.995	560.9	14.3	104.3	0.663	525.4	15.1	97.7	0.965	531.3	14.7	98.8	0.998
80	550.9	14.2	0.307	567.8	14.8	103.1	0.879	562.6	15.7	102.1	0.975	573.2	14.2	104.0	0.699	535.2	15.3	97.1	0.912	543.2	14.9	98.6	0.996
84	560.0	14.9	0.326	578.2	15.5	103.3	0.867	575.8	16.7	102.8	0.930	583.0	14.8	104.1	0.707	545.8	16.3	97.5	0.952	552.5	15.8	98.7	0.997
88	565.2	16.9	0.519	586.3	17.5	103.7	0.854	593.9	19.0	105.1	0.684	593.4	17.1	105.0	0.650	554.3	18.7	98.1	0.991	565.5	17.9	100.1	1.000
92	564.7	15.6	0.554	597.5	16.0	105.8	0.440	593.6	17.9	105.1	0.617	606.3	16.2	107.4	0.227	556.0	17.3	98.5	0.996	571.0	16.3	101.1	0.999
96	563.5	16.6	0.854	608.6	17.0	108.0	0.206	608.2	19.3	107.9	0.271	624.0	17.4	110.7	0.049	567.0	18.5	100.6	1.000	580.0	17.3	102.9	0.937
100	567.5	18.0	0.625	623.8	17.8	109.9	0.103	619.9	20.6	109.2	0.201	637.6	18.8	112.4	0.031	566.9	20.3	99.9	1.000	583.0	18.6	102.7	0.964
104	563.2	20.0	0.644	629.3	19.6	111.7	0.074	633.4	22.8	112.5	0.082	643.9	21.6	114.3	0.026	561.0	23.1	99.6	1.000	585.5	22.7	104.0	0.918

¹ All p-values and % are relative to the 0 dose control group, except p-value for trend shown below control.

Analysis of Terminal Sacrifice Body Weight Data

*Table 11. ANOVA Results for Body Weight Terminal Sacrifice
Male Bisphenol-A Continuous Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)*

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	5	286	1.764	0.120
Week	25	5918	2074.826	<.001
Dose*Week	125	5918	0.418	0.999

Analysis of Terminal Sacrifice Body Weight Data

Table 12. Comparisons of Least Squares Means for Body Weight Terminal Sacrifice Male Bisphenol-A Continuous Dose Arm¹

Week	Dose ($\mu\text{g}/\text{kg}/\text{bw}/\text{day}$)																							
	0				2.5				25				250				2500				25000			
	Mean	SE	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	Mean	SE	Pct	P value	
4	83.9	1.2	0.885	84.0	1.2	100.1	1.000	85.6	1.2	102.1	0.730	83.9	1.2	100.1	1.000	81.5	1.2	97.2	0.472	85.4	1.2	101.8	0.834	
8	294.9	3.9	0.655	301.7	3.9	102.3	0.609	297.0	3.9	100.7	0.995	290.5	3.9	98.5	0.892	292.5	3.9	99.2	0.992	304.6	4.0	103.3	0.280	
12	428.3	5.5	0.758	434.5	5.6	101.5	0.890	424.9	5.6	99.2	0.991	418.7	5.4	97.8	0.598	420.1	5.4	98.1	0.730	435.3	5.7	101.6	0.840	
16	502.4	6.7	0.701	506.3	6.9	100.8	0.994	495.8	6.8	98.7	0.938	492.1	6.7	98.0	0.716	495.8	6.7	98.7	0.934	505.1	7.0	100.5	0.999	
20	549.8	7.7	0.610	557.3	7.9	101.4	0.938	545.9	7.8	99.3	0.997	542.6	7.7	98.7	0.949	542.8	7.7	98.7	0.954	552.4	8.0	100.5	0.999	
24	585.3	8.4	0.578	591.3	8.5	101.0	0.984	583.3	8.6	99.7	1.000	580.7	8.4	99.2	0.995	576.9	8.4	98.6	0.932	586.4	8.7	100.2	1.000	
28	613.6	9.3	0.520	621.8	9.4	101.3	0.959	609.1	9.4	99.3	0.997	612.1	9.3	99.8	1.000	603.2	9.3	98.3	0.894	614.0	9.7	100.1	1.000	
32	638.6	10.2	0.526	644.6	10.3	100.9	0.993	631.2	10.3	98.8	0.981	640.6	10.1	100.3	1.000	625.3	10.1	97.9	0.820	637.4	10.5	99.8	1.000	
36	657.2	9.4	0.459	664.1	9.6	101.0	0.981	652.1	9.5	99.2	0.995	660.7	9.3	100.5	0.999	643.0	9.3	97.8	0.722	656.4	9.7	99.9	1.000	
40	676.6	10.0	0.345	686.4	10.1	101.4	0.937	671.4	10.0	99.2	0.996	681.8	9.9	100.8	0.996	660.2	9.9	97.6	0.654	674.3	10.3	99.7	1.000	
44	693.7	10.5	0.269	704.4	10.7	101.5	0.929	687.5	10.5	99.1	0.992	702.8	10.4	101.3	0.960	677.2	10.4	97.6	0.689	687.4	10.8	99.1	0.992	
48	709.6	11.1	0.408	721.0	11.3	101.6	0.926	703.5	11.1	99.1	0.994	723.6	11.0	102.0	0.838	695.2	10.9	98.0	0.819	705.6	11.4	99.4	0.999	
52	727.2	11.5	0.521	736.5	11.7	101.3	0.971	719.2	11.6	98.9	0.985	745.1	11.4	102.5	0.701	711.0	11.4	97.8	0.774	724.8	11.9	99.7	1.000	
56	743.7	12.3	0.648	754.1	12.6	101.4	0.967	739.1	12.3	99.4	0.999	765.5	12.3	102.9	0.594	727.9	12.2	97.9	0.830	744.6	12.8	100.1	1.000	
60	756.4	13.2	0.939	771.9	13.4	102.1	0.877	751.9	13.2	99.4	0.999	783.5	13.2	103.6	0.450	745.0	13.1	98.5	0.961	764.5	13.8	101.1	0.992	
64	771.5	13.9	0.987	791.9	14.2	102.6	0.757	770.9	14.0	99.9	1.000	802.5	14.0	104.0	0.377	756.6	13.9	98.1	0.911	786.0	14.7	101.9	0.928	
68	789.2	14.8	0.908	813.2	15.1	103.0	0.678	792.2	14.9	100.4	1.000	816.8	14.9	103.5	0.546	778.3	14.8	98.6	0.980	808.1	15.7	102.4	0.849	
72	804.1	15.5	0.869	832.3	15.8	103.5	0.576	808.2	15.6	100.5	1.000	834.5	15.6	103.8	0.500	794.2	15.5	98.8	0.989	826.0	16.4	102.7	0.792	
76	812.7	16.5	0.764	850.2	16.8	104.6	0.365	824.3	16.8	101.4	0.984	851.0	16.8	104.7	0.342	810.5	16.6	99.7	1.000	839.7	17.7	103.3	0.695	
80	825.2	17.4	0.888	867.0	17.6	105.1	0.307	834.1	17.7	101.1	0.996	861.6	17.5	104.4	0.436	822.3	17.5	99.7	1.000	850.6	18.6	103.1	0.774	
84	833.0	18.0	0.637	875.5	18.0	105.1	0.318	837.9	18.6	100.6	1.000	872.6	18.0	104.8	0.383	832.6	18.1	99.9	1.000	866.4	19.3	104.0	0.584	
88	832.4	18.6	0.677	873.2	18.3	104.9	0.380	842.7	19.3	101.2	0.995	877.6	18.5	105.4	0.289	830.2	18.7	99.7	1.000	864.6	20.1	103.9	0.651	
92	831.4	19.2	0.688	862.7	18.6	103.8	0.651	851.6	19.8	102.4	0.921	883.0	19.3	106.2	0.209	823.4	19.2	99.0	0.999	861.9	20.6	103.7	0.716	
96	825.1	20.4	0.468	859.7	19.7	104.2	0.618	849.4	21.0	102.9	0.876	893.9	20.4	108.3	0.070	822.6	20.3	99.7	1.000	864.2	22.6	104.7	0.572	
100	815.6	23.0	0.230	850.6	22.2	104.3	0.706	846.2	23.3	103.8	0.816	890.1	22.7	109.1	0.084	822.0	22.9	100.8	1.000	872.2	26.0	106.9	0.340	
104	807.5	23.5	0.182	847.0	23.4	104.9	0.640	838.3	24.1	103.8	0.828	889.4	24.2	110.2	0.062	830.6	23.9	102.9	0.937	862.8	27.2	106.8	0.397	

¹ All p-values and % are relative to the 0 dose control group, except p-value for trend shown below control.

Analysis of Terminal Sacrifice Body Weight Data

c) *EE₂ Treatments Continuous Dose*

**Table 13. Summary Statistics for Terminal Sacrifice
Female Body Weight Ethinyl Estradiol Dose**

		<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>								
		<i>0</i>			<i>0.05</i>			<i>0.5</i>		
<i>Week</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	
4	50	75.4	0.9	26	76.5	1.4	26	80.1	1.8	
8	50	196.0	2.6	26	199.5	3.9	26	211.7	3.9	
12	50	266.1	3.9	26	269.2	5.5	26	268.1	5.5	
16	50	302.5	5.0	26	298.9	6.3	26	298.8	6.7	
20	50	324.4	5.7	26	320.0	6.9	26	319.7	8.8	
24	50	342.3	6.3	26	339.2	7.9	26	338.0	9.9	
28	50	358.8	6.8	26	351.0	8.3	26	354.5	11.3	
32	50	372.4	7.6	26	365.5	8.6	26	373.3	12.3	
36	50	387.2	8.1	26	375.2	9.3	26	389.9	13.1	
40	50	401.7	8.8	26	391.8	10.3	26	405.8	13.2	
44	50	417.3	9.5	26	403.3	11.4	26	421.0	13.6	
48	50	430.9	9.9	26	417.9	11.3	26	438.8	14.7	
52	50	447.2	10.5	26	432.9	12.1	26	449.7	15.4	
56	50	463.0	11.2	26	449.6	12.6	25	458.9	16.3	
60	50	478.4	11.6	26	462.4	13.3	25	475.3	18.3	
64	49	495.1	12.0	26	477.4	14.0	25	484.8	19.5	
68	47	506.4	12.3	24	496.7	15.4	24	491.6	22.6	
72	44	519.7	13.5	21	521.0	16.4	22	506.5	24.3	
76	40	530.9	15.5	17	530.3	19.3	21	521.3	26.3	
80	39	542.5	16.4	15	543.7	18.5	17	531.4	34.0	
84	35	533.0	15.0	14	552.0	19.5	15	550.9	39.6	
88	32	534.0	17.5	13	538.8	22.9	11	563.7	50.7	
92	26	530.1	15.3	12	561.1	21.9	8	512.1	27.1	
96	23	531.3	16.8	10	563.4	25.9	7	524.6	33.5	
100	17	536.6	20.6	7	597.2	33.7	6	542.4	36.0	
104	17	534.1	22.3	7	602.0	34.7	4	562.1	49.5	

Analysis of Terminal Sacrifice Body Weight Data

<i>Table 14. Summary Statistics for Terminal Sacrifice Male Body Weight Ethinyl Estradiol Dose</i>									
<i>Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)</i>									
		<i>0</i>		<i>0.05</i>		<i>0.5</i>			
<i>Week</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>
4	50	83.9	1.2	26	82.2	2.0	26	87.9	2.1
8	50	294.9	3.9	26	296.8	5.4	26	306.0	5.4
12	49	428.8	7.0	26	427.6	7.8	26	431.3	7.7
16	49	503.0	9.5	26	503.8	10.0	26	502.4	10.1
20	49	550.3	11.3	26	553.3	11.3	26	548.6	11.5
24	49	585.9	12.1	26	586.1	12.7	26	580.7	11.3
28	49	614.2	14.2	26	613.7	13.1	24	608.3	13.0
32	49	639.2	15.9	26	636.9	14.2	26	631.8	13.1
36	48	646.9	10.1	26	657.8	15.7	26	655.0	14.0
40	48	666.8	10.5	26	678.1	16.1	26	673.0	15.3
44	47	684.1	11.4	26	695.6	16.7	26	692.0	15.8
48	47	700.5	11.8	26	711.8	17.8	26	709.6	16.6
52	47	718.6	12.7	26	726.4	19.6	26	725.5	17.5
56	47	735.5	13.0	24	753.7	20.3	26	742.2	17.6
60	47	748.5	13.4	23	782.9	19.2	26	759.8	18.3
64	46	765.2	13.9	23	802.6	20.7	25	771.2	20.5
68	45	783.3	15.1	22	828.4	22.3	24	787.6	25.7
72	42	792.5	16.7	22	848.3	23.9	22	806.5	23.8
76	41	801.1	18.8	22	864.4	24.4	21	832.3	24.5
80	38	818.9	19.1	20	873.1	27.0	20	855.0	25.4
84	34	826.6	20.9	18	889.4	28.9	19	853.9	24.8
88	30	826.3	23.4	15	916.6	28.4	16	870.2	27.3
92	26	822.6	27.1	14	924.8	31.1	17	871.7	27.4
96	23	831.2	29.8	13	925.2	34.5	16	872.8	28.4
100	20	822.7	36.5	10	926.0	42.4	15	888.4	29.7
104	18	817.6	40.1	9	900.9	53.0	13	852.7	23.0

Analysis of Terminal Sacrifice Body Weight Data

**Table 15. ANOVA Results for Body Weight Terminal Sacrifice
Female Ethinyl Estradiol Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)**

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	2	99	0.276	0.759
Week	25	2046	457.710	<.001
Dose*Week	50	2046	1.399	0.034

Analysis of Terminal Sacrifice Body Weight Data

**Table 16. Comparisons of Least Squares Means for Body Weight
Terminal Sacrifice Female Ethinyl Estradiol Dose¹**

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)									
	0		0.05				0.5			
	Mean	SE	Mean	SE	Pct	P value	Mean	SE	Pct	P value
4	75.4	1.1	76.5	1.5	101.5	0.764	80.0	1.5	106.2	0.019
8	196.0	2.7	199.5	3.8	101.8	0.663	211.6	3.8	108.0	0.002
12	266.1	3.9	269.2	5.5	101.1	0.862	268.0	5.4	100.7	0.947
16	302.5	4.8	298.9	6.7	98.8	0.866	298.6	6.7	98.7	0.849
20	324.4	5.7	320.0	7.9	98.6	0.862	319.5	7.9	98.5	0.831
24	342.3	6.4	339.2	8.9	99.1	0.942	337.7	8.9	98.6	0.877
28	358.8	7.0	351.0	9.7	97.8	0.741	354.1	9.7	98.7	0.897
32	372.4	7.6	365.5	10.6	98.2	0.820	372.9	10.6	100.1	0.999
36	387.2	8.2	375.2	11.3	96.9	0.598	389.4	11.3	100.6	0.982
40	401.7	8.7	391.8	12.0	97.5	0.729	405.2	12.0	100.9	0.960
44	417.3	9.3	403.3	12.8	96.6	0.580	420.2	12.8	100.7	0.974
48	430.9	9.7	417.9	13.4	97.0	0.647	438.0	13.4	101.6	0.875
52	447.2	10.2	432.9	14.2	96.8	0.626	448.8	14.2	100.3	0.994
56	463.0	10.8	449.6	14.9	97.1	0.686	460.1	14.9	99.4	0.982
60	478.4	11.5	462.4	15.9	96.7	0.627	476.3	16.0	99.6	0.991
64	494.6	12.0	477.4	16.6	96.5	0.609	485.4	16.7	98.1	0.864
68	509.7	12.8	492.5	17.7	96.6	0.644	491.8	17.7	96.5	0.623
72	524.1	13.4	506.9	18.8	96.7	0.675	501.9	18.7	95.8	0.524
76	538.0	14.9	520.7	21.4	96.8	0.732	509.8	20.6	94.8	0.433
80	551.8	16.1	538.6	23.6	97.6	0.857	520.7	22.3	94.4	0.421
84	559.6	16.1	550.3	24.2	98.3	0.927	531.1	22.9	94.9	0.491
88	563.5	17.5	544.2	26.5	96.6	0.767	531.0	25.6	94.2	0.471
92	556.6	12.9	559.2	19.4	100.5	0.991	541.6	20.6	97.3	0.762
96	557.0	14.1	566.2	21.3	101.7	0.910	542.4	22.6	97.4	0.807
100	563.3	16.4	575.6	25.0	102.2	0.883	540.5	26.7	96.0	0.687
104	559.9	18.6	581.2	28.6	103.8	0.757	547.8	32.8	97.8	0.928

¹ All p-values and % are relative to the 0 dose control group

Analysis of Terminal Sacrifice Body Weight Data

**Table 17. ANOVA Results for Body Weight Terminal Sacrifice
Male Ethinyl Estradiol Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)**

<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P value</i>
Dose	2	99	0.721	0.488
Week	25	2080	780.082	<.001
Dose*Week	50	2080	0.364	0.999

Analysis of Terminal Sacrifice Body Weight Data

Table 18. Comparisons of Least Squares Means for Body Weight Terminal Sacrifice Male Ethinyl Estradiol Dose¹

Week	Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)									
	0			0.05			0.5			
	Mean	SE	Mean	SE	Pct	P value	Mean	SE	Pct	P value
4	83.9	1.3	82.2	1.9	98.1	0.704	88.0	1.8	104.9	0.135
8	294.9	3.9	296.8	5.4	100.7	0.938	306.2	5.3	103.8	0.152
12	428.2	6.3	427.6	8.7	99.9	0.997	431.8	8.6	100.8	0.923
16	502.3	8.4	503.8	11.7	100.3	0.992	503.0	11.5	100.2	0.998
20	549.6	9.9	553.3	13.6	100.7	0.965	549.5	13.4	100.0	1.000
24	585.2	10.5	586.1	14.5	100.2	0.998	581.7	14.3	99.4	0.972
28	613.5	11.9	613.7	16.4	100.0	1.000	612.2	16.1	99.8	0.997
32	638.5	13.1	636.9	18.1	99.7	0.996	632.8	17.4	99.1	0.951
36	655.7	10.4	657.8	14.3	100.3	0.990	655.4	14.0	100.0	1.000
40	675.1	11.0	678.1	15.1	100.4	0.981	673.9	14.6	99.8	0.997
44	692.3	11.6	695.6	15.8	100.5	0.980	692.9	15.4	100.1	0.999
48	708.3	12.2	711.8	16.6	100.5	0.979	710.5	16.3	100.3	0.991
52	726.2	13.2	726.4	17.9	100.0	1.000	726.7	17.5	100.1	0.999
56	742.3	13.3	740.9	18.2	99.8	0.997	743.3	17.8	100.1	0.999
60	754.7	13.4	763.4	18.4	101.2	0.898	760.9	17.9	100.8	0.944
64	769.9	14.2	784.1	19.7	101.8	0.784	772.8	19.0	100.4	0.989
68	787.9	15.9	804.7	22.2	102.1	0.761	787.3	21.2	99.9	1.000
72	802.6	16.3	826.8	22.7	103.0	0.592	801.1	22.0	99.8	0.998
76	811.3	17.4	843.9	24.1	104.0	0.443	820.5	23.6	101.1	0.931
80	823.8	17.9	857.9	24.8	104.1	0.428	836.4	24.4	101.5	0.882
84	831.7	18.5	868.6	25.5	104.4	0.396	847.8	25.0	101.9	0.824
88	831.3	19.0	876.4	26.4	105.4	0.280	861.0	25.6	103.6	0.546
92	831.0	21.3	893.9	29.4	107.6	0.148	867.9	27.2	104.4	0.459
96	824.7	23.0	890.9	31.5	108.0	0.159	870.5	29.1	105.6	0.358
100	814.9	26.8	893.5	37.1	109.6	0.152	877.3	32.5	107.7	0.239
104	806.2	29.2	874.4	40.6	108.5	0.292	861.7	35.4	106.9	0.374

¹ All p-values and % are relative to the 0 dose control group

B. Figures

Figure 1. Body Weight (g) for Terminal Sacrifice Females in the BPA Stop Dose Arm

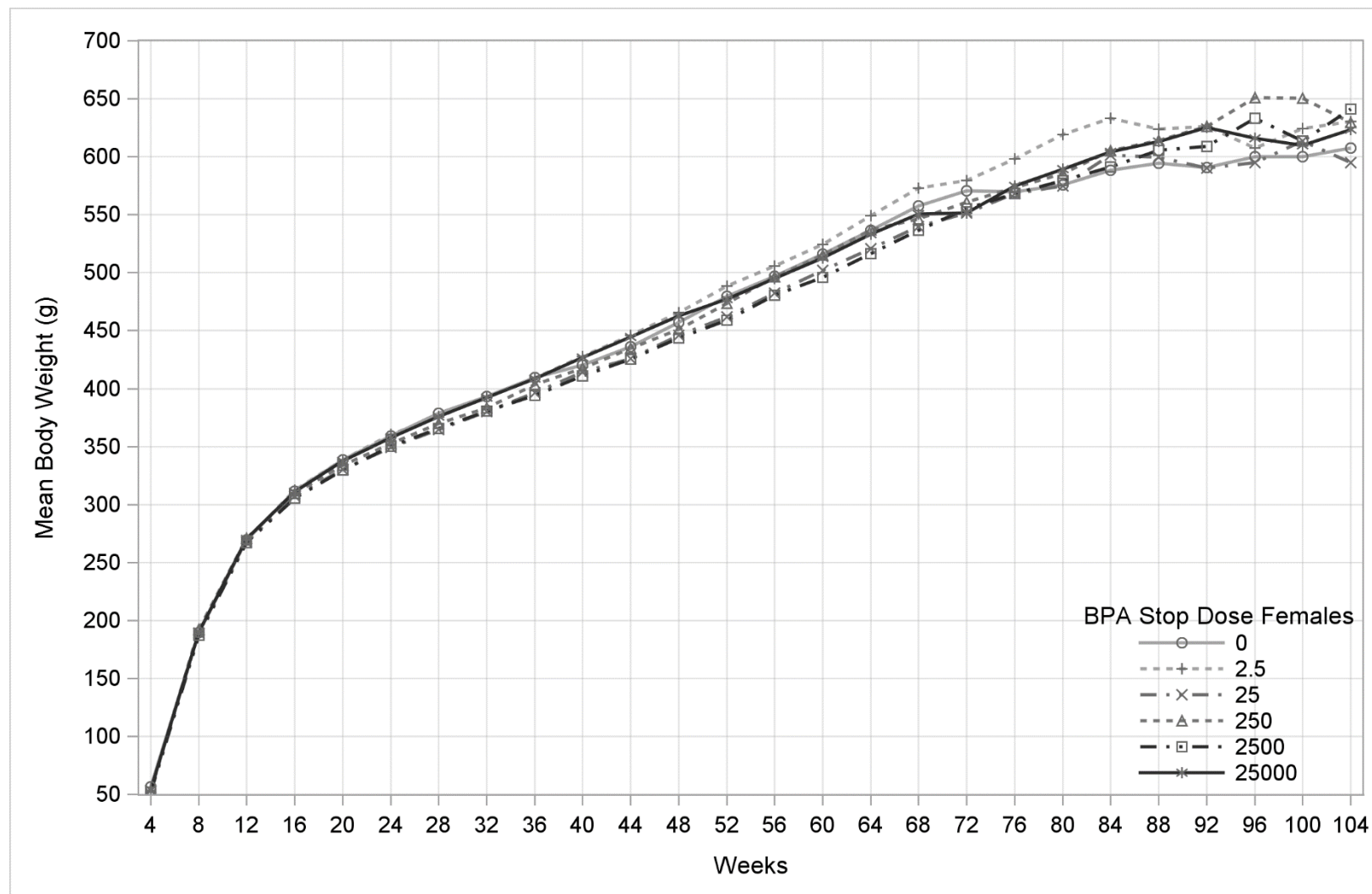


Figure 2. Body Weight (g) for Terminal Sacrifice Males in the BPA Stop Dose Arm

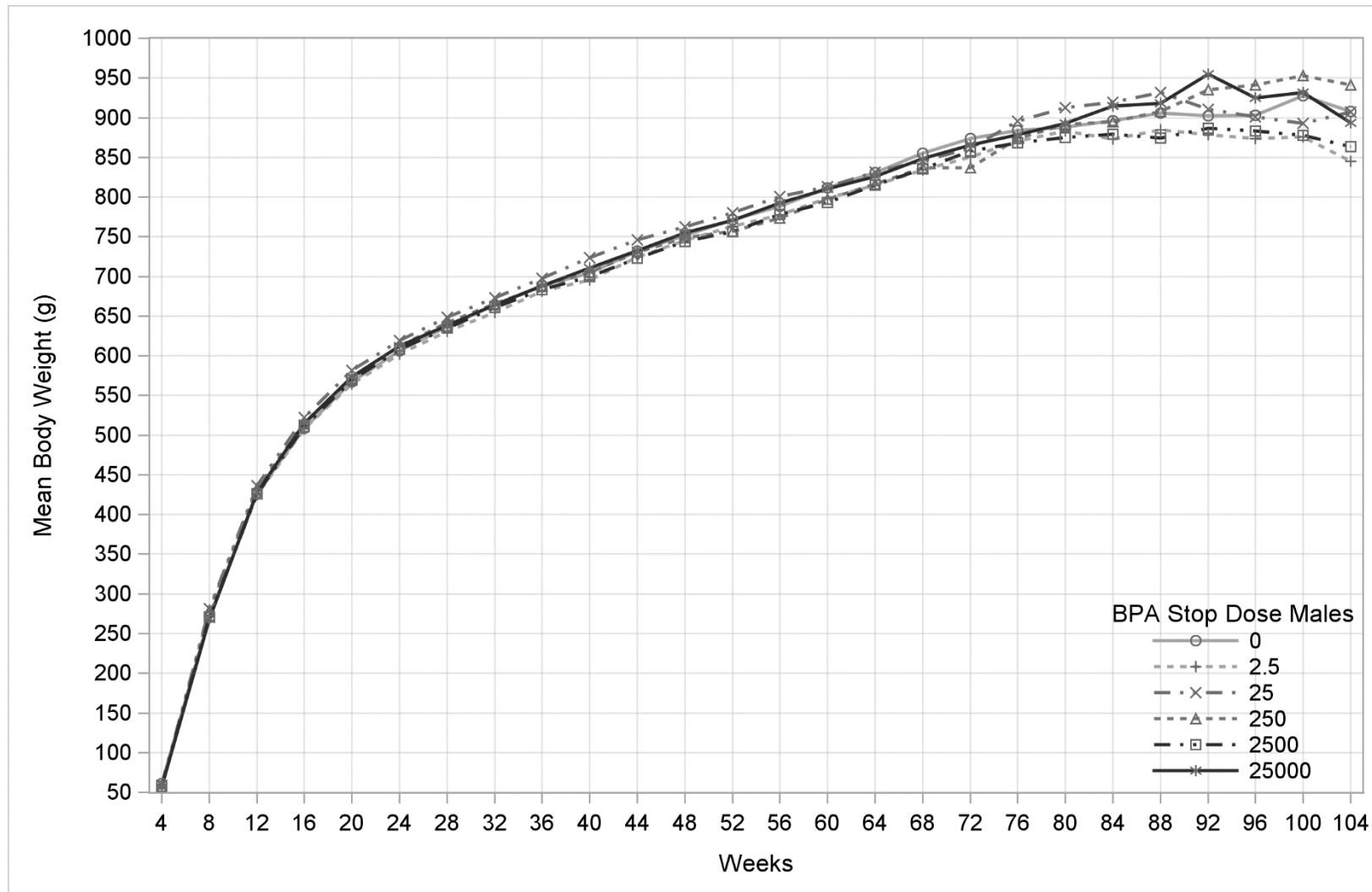


Figure 3. Body Weight (g) for Terminal Sacrifice Females in the BPA Continuous Dose Arm

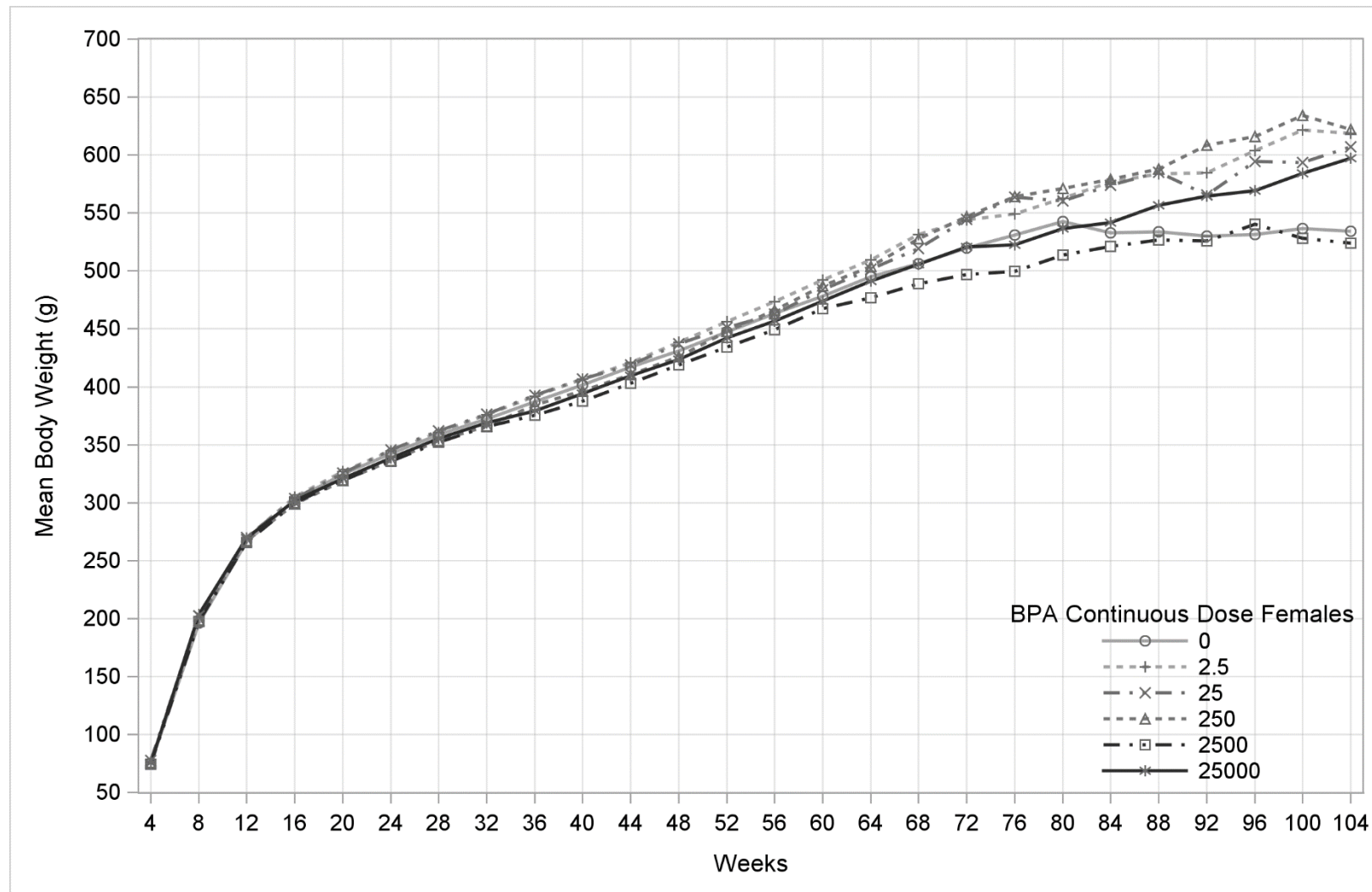


Figure 4. Body Weight (g) for Terminal Sacrifice Males in the BPA Continuous Dose Arm

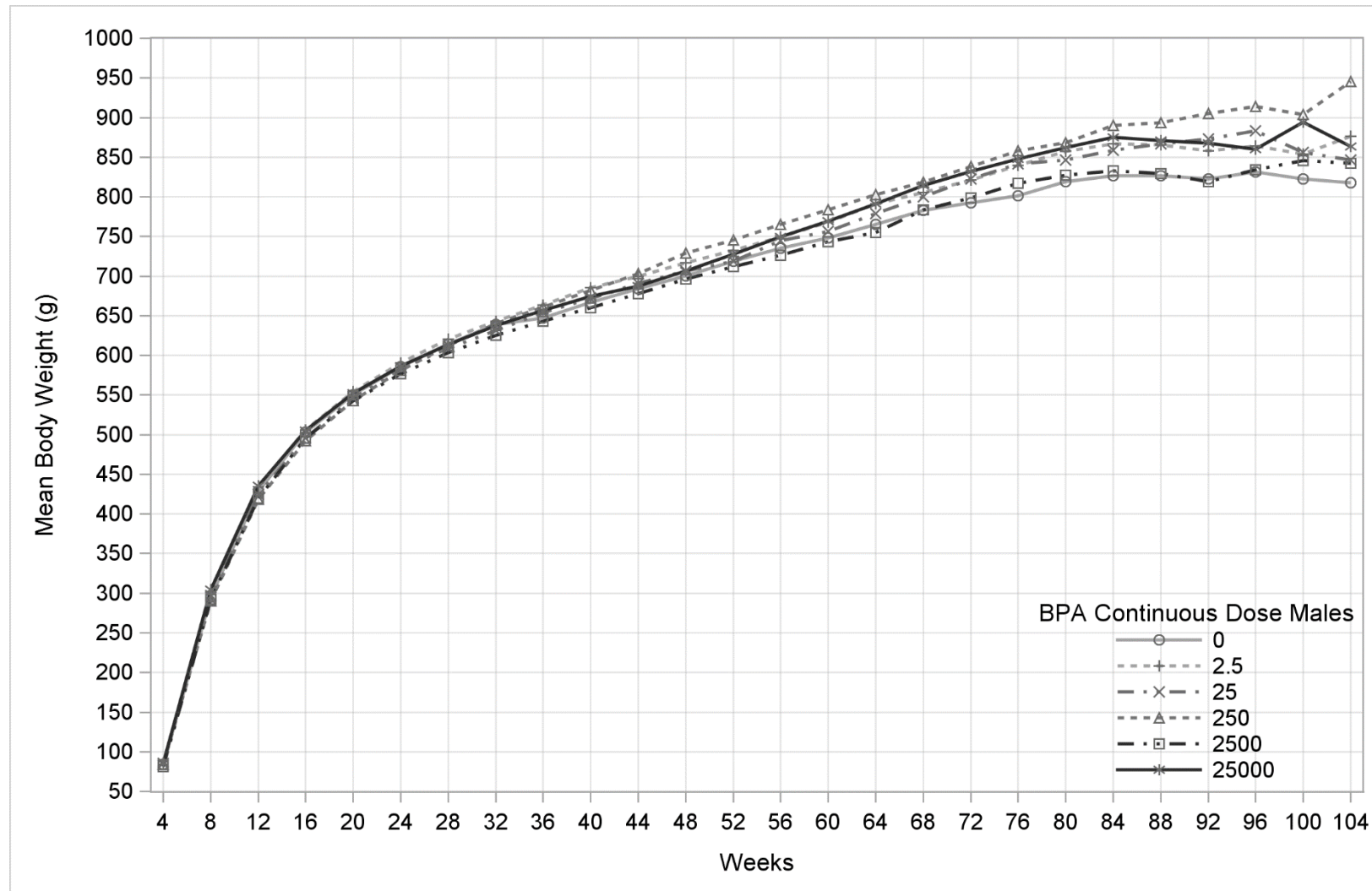


Figure 5. Body Weight (g) for Terminal Sacrifice Females EE₂ Continuous Dose

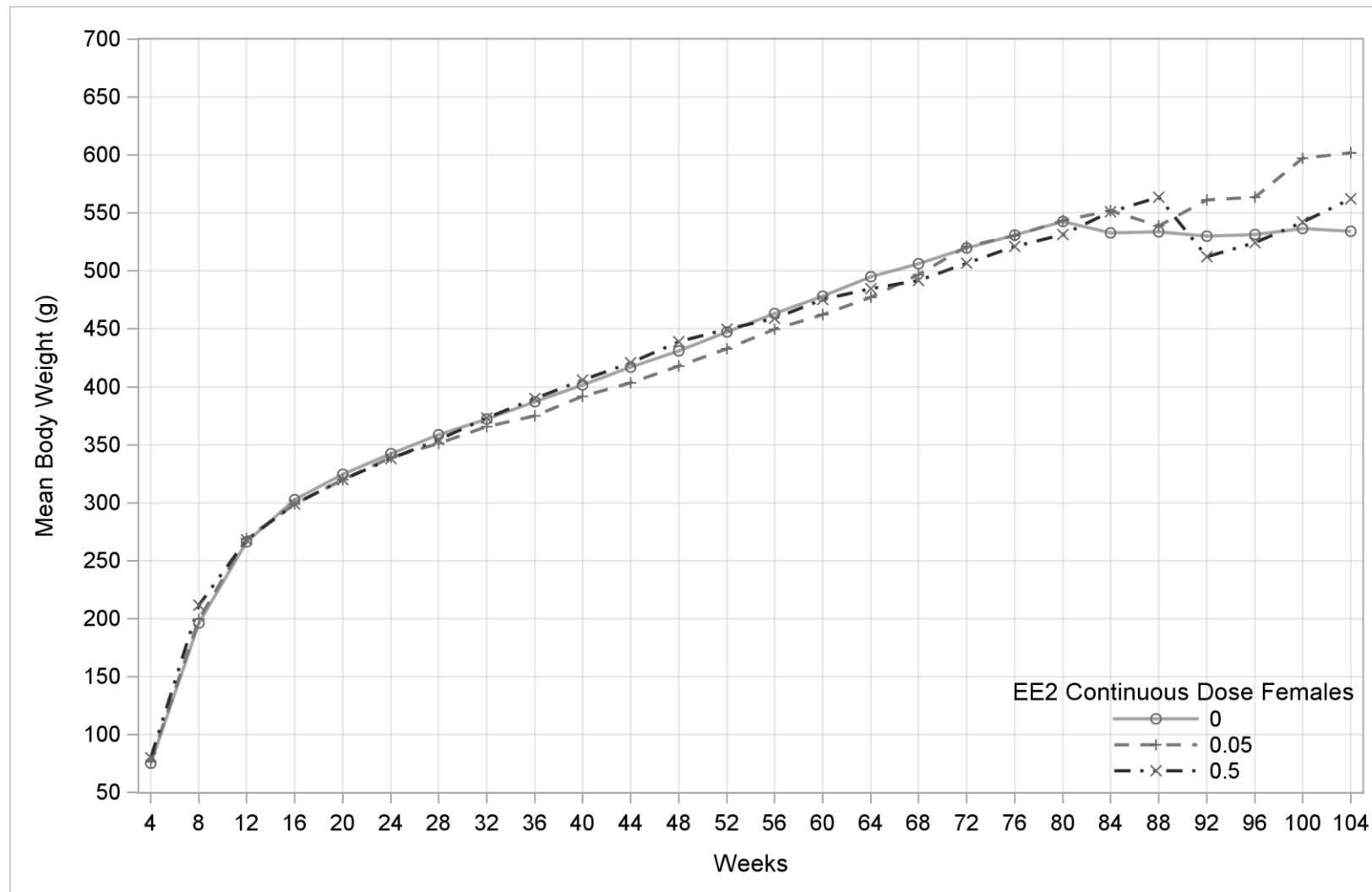
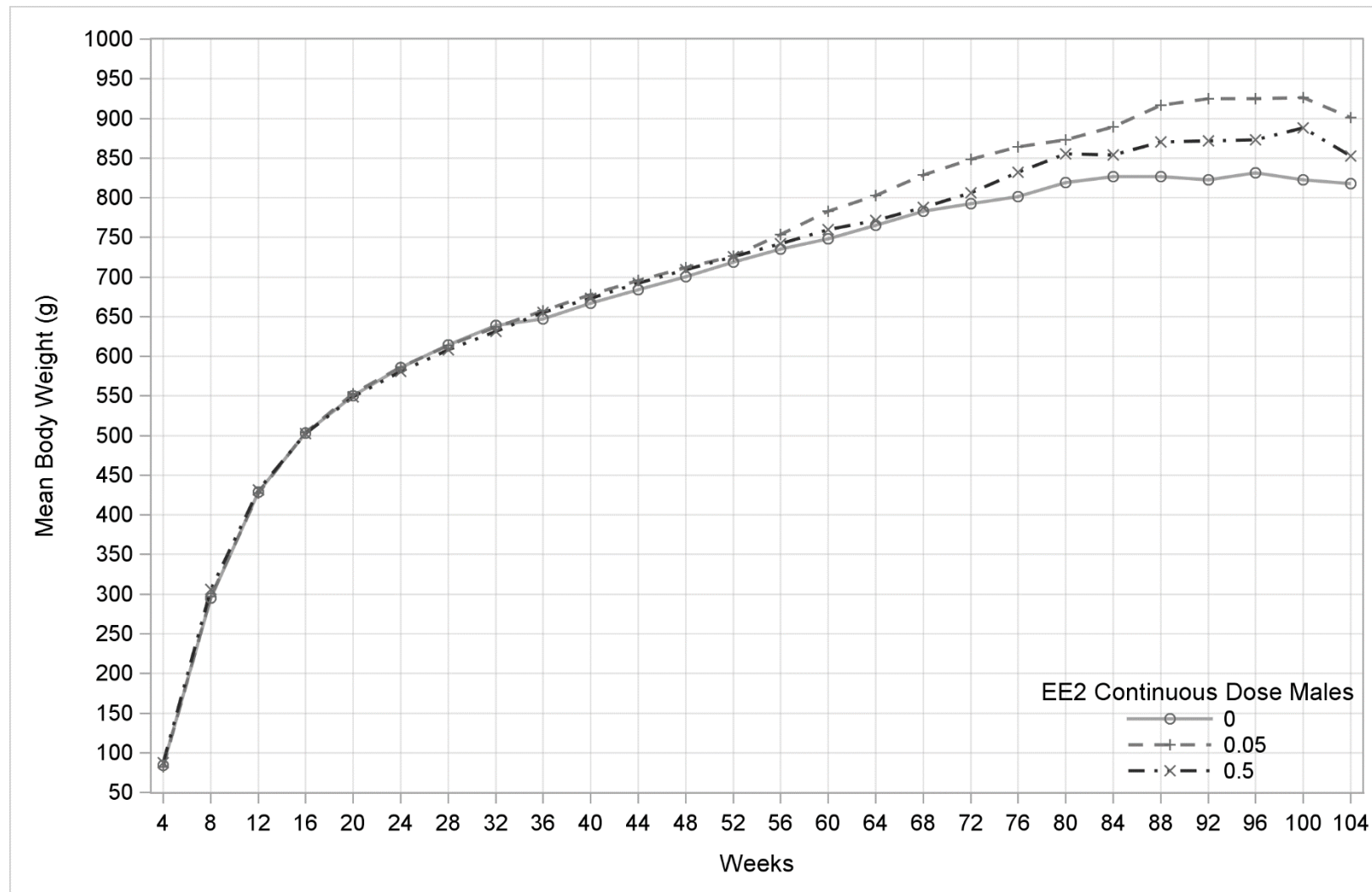


Figure 6. Body Weight (g) for Terminal Sacrifice Males EE₂ Continuous Dose



C. Outliers

Table 1. Outliers¹ for Terminal Sacrifice Body Weight Bisphenol-A Stop-Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)

<i>Sex</i>	<i>UIN</i>	<i>Dose</i>	<i>Week</i>	<i>Weight (g)</i>	<i>Difference (g)²</i>
F	23000534214	0	40	353.0	-190.7
	23000534438	0	40	547.0	184.4
	23000531605	25000	72	606.7	-75.4
	23000531622	25000	72	696.4	94.9
M	23000533533	0	68	673.1	-68.0
	23000528936	0	76	784.3	70.9
	23000535053	0	80	569.4	-95.7
	23000529291	0	104	1190.7	87.6
	23000533226	2.5	76	655.4	-76.1
	23000533915	25	44	745.8	165.9
	23000530518	250	64	614.1	-82.1
	23000534278	250	80	691.5	-90.3
	23000530656	25000	20	501.1	-120.7
	23000530697	25000	20	634.7	125.2
	23000533114	25000	68	600.6	-70.9
	23000528414	25000	96	1064.4	-95.5

¹ For each animal, the observed post-weaning body weight was compared to the predicted body weight using a 5-point running median smoother and nearest neighbor interpolation.

² The threshold for outlier exclusion was a difference between the observed and predicted weights greater than 60 (g) for females and 65 (g) for males with graphical confirmation for week 4.

Table 2. Outliers¹ for Terminal Sacrifice Body Weight Bisphenol-A Continuous

<i>Sex</i>	<i>UIN</i>	<i>Dose</i>	<i>Week</i>	<i>Weight (g)</i>	<i>Difference (g)²</i>
F	23000532950	25	104	701.3	90.4
M	23000536440	2.5	20	778.3	154.7
	23000536632	2.5	20	429.1	-157.0
	23000534197	25	36	506.9	-70.2
	23000532945	25	96	595.5	-99.1
	23000528217	2500	44	516.9	-76.1
	23000533051	2500	76	534.0	-130.3
	23000529372	2500	84	754.2	-89.4
	23000528188	25000	76	915.1	75.2
	23000534397	25000	88	1002.8	-74.5

¹ For each animal, the observed post-weaning body weight was compared to the predicted body weight using a 5-point running median smoother and nearest neighbor interpolation.

² The threshold for outlier exclusion was a difference between the observed and predicted weights greater than 60 (g) for females and 65 (g) for males with graphical confirmation for week 4.

Table 3. Outliers¹ for Terminal Sacrifice Body Weight Ethinyl Estradiol ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)

<i>Sex</i>	<i>UIN</i>	<i>Dose</i>	<i>Week</i>	<i>Weight (g)</i>	<i>Difference (g)²</i>
F	23000534814	0.5	76	298.8	-82.9
M	23000530665	0.5	28	597.3	-79.8
	23000530840	0.5	28	683.2	77.0
	23000532690	0.5	88	934.0	113.2
	23000532753	0.5	88	805.9	-117.2

¹ For each animal, the observed post-weaning body weight was compared to the predicted body weight using a 5-point running median smoother and nearest neighbor interpolation.

² The threshold for outlier exclusion was a difference between the observed and predicted weights greater than 60 (g) for females and 65 (g) for males with graphical confirmation for week 4.

D. Data

Body weight data were extracted from the Genesis database using SAS Proc SQL, utilizing the Vortex ODBC driver.

Quality Control

1. *Data Verification*

The extraction of the data into SAS was verified by the statistical reviewer by review of the SAS code used to extract and verify the data.

2. *Computer Program Verification*

SAS programs were used to extract the data, explore the distributional properties of the data, and perform the statistical analysis.

The SAS programs were verified by detailed review of the program code, the program log, and the program output.

3. *Statistical Report Review*

3.1 *Statistical Report Text*

The statistical report was reviewed for logic, internal completeness, technical appropriateness, technical accuracy, and grammar. Technical appropriateness was reviewed based on statistical expertise.

Comments and questions were provided from the reviewer to the statistician. The statistician made appropriate changes and returned the report to the reviewer for final verification.

The text of the final statistical report was considered by the reviewer to be logical, internally complete, and technically appropriate and accurate. The statistical results stated in the text accurately presented those in the tables.

3.2 *Table Verification*

Analysis results were output from SAS to an .rtf file using PROC REPORT, which were then copied into the statistical report.

Statistical report tables were verified by checking the procedure used to create the tables and, additionally, by checking numbers sufficiently to conclude that the tables are correct.

3.3 *Graph Verification*

Graphs were verified by review of the SAS code used to generate them, and by calculation of summary statistics and checking numbers sufficiently to conclude that the graphs are correct. Graphs appear to be appropriate and correct.

4. *Conclusions*

The final statistical report has been fully reviewed and is considered by the reviewer to be logical, internally complete, and technically appropriate and accurate.