

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 INTERIM SACRIFICE BODY WEIGHT DATA

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Statistical Analysis of Interim 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 one year body weights based on interim 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 loads. 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 allocated to 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 allocated to 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 52 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, 134 core study 1 year interim sacrifice animals (22 in vehicle control, 84 in BPA 2.5, 25, 250, 2500, and 25000 $\mu\text{g}/\text{kg}$ bw/day, and 28 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 134 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 35 (g) 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 the BPA stop dose arm 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 means are presented in Table 4 for female body weights and in Table 6 for males. There were no significant dose trends or pairwise comparisons of dosed treatments to control for either females or males.

There were no statistically significant results in the sensitivity analysis of BPA stop dose arm for either females or males.

4.2 BPA Treatments Continuous Dose Arm

Summary statistics for the BPA continuous dose arm 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 $p < 0.001$), and treatment effect was significant for females ($p = 0.011$).

Comparisons of least squares mean body weights are presented in Table 10 for females and in Table 12 for males. There were no significant trends or pairwise comparisons of vehicle control to dosed groups for either females or males.

There were no statistically significant results in the sensitivity analysis of BPA continuous dose arm for either females or males.

4.3 *EE₂ Treatments Continuous Dose*

Summary statistics for the EE₂ continuous dose arm 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 ($p = 0.005$).

Comparisons of least squares mean body weights are presented in Table 16 for females and in Table 18 for males. There were no significant dose trends or pairwise comparisons for EE₂ continuous dose 0.05 $\mu\text{g}/\text{kg}$ bw/day or 0.5 $\mu\text{g}/\text{kg}$ bw/day compared to control at any week for either females or males.

There were no statistically significant results in the sensitivity analysis of EE₂ continuous dose arm for either females or males.

5. Conclusions

5.1 *BPA Treatments Stop Dose Arm*

There were no significant differences in comparisons to control for BPA stop dose treatments for females or males.

5.2 *BPA Treatments Continuous Dose Arm*

There were no significant differences in comparisons to control for BPA continuous dose treatments for females or males.

5.3 *EE₂ Treatments Continuous Dose*

There were no significant differences in comparisons to control for EE₂ continuous dose 0.05 $\mu\text{g}/\text{kg}$ bw/day and 0.5 $\mu\text{g}/\text{kg}$ bw/day treatments for females or males.

Appendices

A. Statistical Tables

Analysis of Interim Sacrifice Body Weight Data

a) BPA Treatments Stop Dose Arm

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

		<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																	
		<i>0</i>			<i>2.5</i>			<i>25</i>			<i>250</i>			<i>2500</i>			<i>25000</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>	<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	20	57.9	2.7	22	53.7	2.7	20	55.2	2.6	22	54.4	2.5	20	55.4	2.9	22	50.6	1.9	
8	20	191.7	4.9	22	184.0	3.1	20	189.8	4.3	22	189.6	4.9	20	188.2	5.0	21	183.5	4.5	
12	20	270.1	7.4	20	263.4	5.3	20	269.7	7.0	22	266.3	6.3	20	272.1	7.5	21	261.8	6.3	
16	18	304.3	10.7	22	301.6	5.2	20	305.4	8.7	22	305.1	7.2	20	310.5	8.0	21	303.1	7.9	
20	20	330.6	11.4	22	329.0	6.8	20	327.5	10.4	22	329.8	8.4	20	338.1	10.4	21	326.1	8.3	
24	20	350.9	12.2	22	349.7	8.1	20	344.3	11.2	22	347.6	8.5	20	358.3	11.8	21	344.1	8.9	
28	20	368.7	12.5	22	366.3	8.8	20	360.4	11.9	22	368.3	10.5	20	372.9	13.5	21	360.8	8.7	
32	20	385.8	14.0	20	391.0	10.2	20	373.7	13.3	22	381.0	11.4	20	391.6	14.8	21	373.8	9.6	
36	20	400.4	14.3	22	398.6	10.4	20	389.4	14.7	22	399.3	13.3	20	403.9	15.3	21	386.4	10.5	
40	18	410.2	16.2	22	419.2	11.5	20	404.5	15.6	20	418.3	15.3	20	421.3	16.6	20	406.6	12.2	
44	20	438.6	16.7	22	432.6	12.3	20	419.1	16.1	22	430.9	15.8	20	437.7	18.2	20	420.5	12.3	
48	20	458.6	18.0	22	453.1	13.7	20	435.6	17.2	22	449.4	17.9	20	451.6	18.2	20	440.1	13.2	
52	20	477.3	19.4	22	468.5	14.5	20	449.7	19.1	22	467.5	19.5	20	466.1	19.0	20	454.9	14.1	

Analysis of Interim Sacrifice Body Weight Data

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

		<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																				
		<i>0</i>		<i>2.5</i>		<i>25</i>		<i>250</i>		<i>2500</i>		<i>25000</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>	<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>	<i>N</i>	<i>Mean</i>	<i>SE</i>	
4	20	61.3	2.1	20	57.9	3.0	20	58.6	2.7	19	59.7	3.1	20	56.8	2.6	22	60.7	2.0				
8	20	274.3	7.0	20	268.7	7.7	20	271.2	5.7	19	270.3	8.9	20	260.9	6.1	22	277.1	4.4				
12	20	423.6	11.2	20	431.7	9.4	20	426.1	6.9	19	430.1	12.3	20	413.2	8.0	22	436.0	7.7				
16	20	505.4	13.6	20	528.9	12.1	20	512.1	9.0	19	514.9	14.1	20	502.9	10.7	22	521.5	8.9				
20	20	561.0	15.1	20	587.0	13.7	19	572.5	11.2	19	565.8	15.1	20	559.5	11.6	22	580.6	9.8				
24	20	596.8	16.4	20	627.5	16.2	19	610.0	11.9	19	603.3	15.7	20	592.8	11.0	22	618.0	10.7				
28	20	626.8	18.2	20	657.7	17.3	18	642.1	14.1	19	629.6	16.6	20	622.7	13.7	22	644.6	11.8				
32	20	651.5	19.1	20	685.0	18.2	19	670.6	15.0	19	655.0	17.8	20	650.8	15.2	22	667.1	12.3				
36	20	675.3	20.6	20	709.5	18.6	17	701.1	18.3	19	677.1	19.1	20	673.5	17.0	22	685.4	12.8				
40	18	683.7	21.9	19	736.8	21.0	19	717.1	17.6	18	687.2	18.2	20	691.5	17.9	22	708.8	13.7				
44	20	716.8	23.1	20	761.3	21.3	19	737.9	19.0	19	716.2	20.1	20	711.9	18.7	22	726.0	14.8				
48	20	731.0	24.9	19	782.7	23.2	19	757.9	21.5	19	735.0	21.6	20	734.6	20.3	22	743.1	15.6				
52	20	752.8	26.5	20	802.6	22.8	19	774.6	22.6	18	743.2	22.9	20	751.1	21.5	22	759.3	16.6				

Analysis of Interim Sacrifice Body Weight Data

Table 3. ANOVA Results for Body Weight Interim Sacrifice Female Bisphenol-A Stop-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	120	0.342	0.886
Week	12	1414	1610.142	<.001
Dose*Week	60	1414	0.268	0.999

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

<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																							
<i>0</i>		<i>2.5</i>				<i>25</i>				<i>250</i>				<i>2500</i>				<i>25000</i>					
<i>Week</i>	<i>Mean</i>	<i>SE</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>
4	57.9	2.6	0.129	53.7	2.5	92.8	0.660	55.2	2.6	95.4	0.921	54.4	2.5	94.0	0.793	55.4	2.6	95.7	0.942	50.6	2.5	87.4	0.157
8	191.7	4.5	0.460	184.1	4.3	96.0	0.628	189.8	4.6	99.0	0.999	189.6	4.3	98.9	0.998	188.2	4.6	98.2	0.978	183.7	4.4	95.8	0.587
12	270.0	6.7	0.765	263.1	6.3	97.5	0.915	269.7	6.7	99.9	1.000	266.3	6.4	98.6	0.994	272.1	6.7	100.8	1.000	262.0	6.4	97.0	0.858
16	308.0	8.0	0.948	301.2	7.4	97.8	0.957	305.4	8.1	99.2	1.000	305.1	7.7	99.0	0.999	310.5	8.1	100.8	1.000	303.4	7.8	98.5	0.992
20	331.4	9.2	0.940	328.4	8.8	99.1	0.999	327.5	9.5	98.8	0.998	329.8	9.1	99.5	1.000	338.1	9.5	102.0	0.984	326.3	9.2	98.5	0.994
24	351.5	10.1	0.952	349.1	9.7	99.3	1.000	344.3	10.4	97.9	0.984	347.6	9.9	98.9	0.999	358.3	10.4	101.9	0.988	344.4	10.0	98.0	0.983
28	369.5	11.1	0.886	365.9	10.6	99.0	1.000	360.4	11.3	97.5	0.970	368.3	10.8	99.7	1.000	372.9	11.3	100.9	1.000	361.0	11.0	97.7	0.976
32	386.7	12.3	0.759	383.3	11.8	99.1	1.000	373.7	12.6	96.6	0.918	381.0	12.0	98.5	0.997	391.6	12.6	101.3	0.999	374.0	12.2	96.7	0.921
36	401.2	13.3	0.692	397.5	12.6	99.1	1.000	389.4	13.5	97.1	0.958	399.3	12.9	99.5	1.000	403.9	13.5	100.7	1.000	386.7	13.1	96.4	0.901
40	420.5	14.7	0.635	417.7	13.8	99.3	1.000	404.5	14.8	96.2	0.906	416.7	14.2	99.1	1.000	421.3	14.8	100.2	1.000	404.4	14.5	96.2	0.900
44	441.3	15.3	0.518	431.3	14.7	97.7	0.987	419.1	15.8	95.0	0.768	431.2	14.9	97.7	0.987	437.7	15.8	99.2	1.000	418.4	15.5	94.8	0.739
48	461.1	16.3	0.459	451.7	15.6	98.0	0.993	435.6	16.7	94.5	0.711	449.7	15.8	97.5	0.983	451.6	16.7	98.0	0.994	438.1	16.4	95.0	0.778
52	480.3	17.5	0.407	467.0	16.7	97.2	0.975	449.7	17.9	93.6	0.614	468.0	16.9	97.4	0.982	466.1	17.9	97.0	0.971	452.9	17.7	94.3	0.704

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

Analysis of Interim Sacrifice Body Weight Data

Table 5. ANOVA Results for Body Weight Interim Sacrifice Male Bisphenol-A Stop-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	115	0.908	0.478
Week	12	1362	1539.715	<.001
Dose*Week	60	1362	0.423	0.999

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

<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																									
		<i>0</i>				<i>2.5</i>				<i>25</i>				<i>250</i>				<i>2500</i>				<i>25000</i>			
<i>Week</i>	<i>Mean</i>	<i>SE</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>		
4	61.3	2.6	0.805	57.9	2.6	94.5	0.826	58.5	2.6	95.5	0.913	59.6	2.7	97.3	0.990	56.8	2.6	92.7	0.616	60.7	2.5	99.0	1.000		
8	274.2	6.7	0.863	268.6	6.7	98.0	0.967	271.1	6.7	98.9	0.997	270.2	6.9	98.5	0.993	260.9	6.7	95.1	0.485	277.1	6.4	101.1	0.998		
12	423.5	9.4	0.887	431.7	9.4	101.9	0.960	426.0	9.4	100.6	1.000	430.0	9.6	101.5	0.986	413.2	9.4	97.6	0.902	436.0	9.0	102.9	0.800		
16	505.3	11.5	0.952	528.9	11.5	104.7	0.457	511.9	11.5	101.3	0.994	514.8	11.8	101.9	0.971	502.9	11.5	99.5	1.000	521.5	11.0	103.2	0.764		
20	560.9	12.8	0.907	587.0	12.8	104.6	0.461	569.2	12.9	101.5	0.989	565.6	13.1	100.8	0.999	559.5	12.8	99.7	1.000	580.6	12.2	103.5	0.696		
24	596.7	13.8	0.989	627.5	13.8	105.2	0.371	606.7	13.9	101.7	0.982	603.1	14.1	101.1	0.998	592.8	13.8	99.3	1.000	618.0	13.1	103.6	0.694		
28	626.7	15.3	0.841	657.7	15.3	104.9	0.464	639.4	15.5	102.0	0.968	629.3	15.7	100.4	1.000	622.7	15.3	99.4	1.000	644.6	14.6	102.9	0.865		
32	651.4	16.3	0.783	685.0	16.3	105.2	0.450	667.9	16.5	102.5	0.929	654.6	16.8	100.5	1.000	650.8	16.3	99.9	1.000	667.1	15.6	102.4	0.934		
36	675.2	17.4	0.591	709.5	17.4	105.1	0.495	697.1	17.7	103.3	0.847	676.7	17.9	100.2	1.000	673.5	17.5	99.8	1.000	685.4	16.6	101.5	0.992		
40	693.7	18.5	0.638	734.0	18.5	105.8	0.392	715.6	18.5	103.2	0.870	696.2	18.9	100.4	1.000	691.5	18.4	99.7	1.000	708.8	17.6	102.2	0.966		
44	716.9	19.4	0.454	760.8	19.5	106.1	0.362	736.4	19.7	102.7	0.931	716.9	20.0	100.0	1.000	711.9	19.7	99.3	1.000	726.0	18.8	101.3	0.997		
48	731.1	20.9	0.583	779.5	21.1	106.6	0.342	756.5	21.3	103.5	0.864	735.9	21.6	100.7	1.000	734.6	21.2	100.5	1.000	743.1	20.2	101.6	0.993		
52	752.5	21.8	0.422	802.9	21.8	106.7	0.338	773.4	22.2	102.8	0.943	750.5	22.5	99.7	1.000	751.1	21.9	99.8	1.000	759.3	20.9	100.9	1.000		

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

Analysis of Interim Sacrifice Body Weight Data

b) BPA Treatments Continuous Dose Arm

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

Week	Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)																		
	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	23	75.6	1.3	22	76.6	1.6	22	75.7	2.3	24	73.6	1.8	20	73.0	1.4	24	75.3	1.6	
8	23	195.7	5.3	22	203.4	4.3	22	204.9	3.9	24	195.8	3.9	20	196.0	3.6	24	197.3	4.0	
12	22	268.0	6.0	22	277.3	5.6	22	277.9	5.8	24	265.5	5.7	20	261.6	4.9	24	262.0	5.6	
16	22	302.0	7.5	22	314.3	7.0	22	316.6	7.0	24	298.8	6.9	20	293.4	4.9	24	292.9	7.4	
20	22	321.7	8.3	22	342.1	9.4	22	345.0	8.2	24	316.5	7.8	20	311.2	6.0	24	315.5	9.5	
24	22	340.4	9.9	22	363.2	11.7	22	362.2	9.4	24	331.3	9.1	20	330.7	5.9	24	331.6	10.8	
28	22	353.8	10.5	22	382.4	13.0	22	380.4	10.6	24	343.6	9.7	20	345.7	6.8	24	350.9	11.9	
32	22	370.1	12.9	22	402.7	14.4	22	394.9	11.3	24	359.7	10.8	20	361.8	7.9	24	365.8	12.8	
36	22	383.8	13.9	22	422.4	16.3	22	409.8	11.9	24	374.4	11.5	20	376.1	8.8	24	378.3	14.0	
40	22	396.2	14.6	22	439.3	18.0	22	422.2	11.9	23	376.7	10.2	20	394.3	10.3	24	395.8	14.5	
44	22	409.7	15.6	22	455.3	19.4	22	433.9	12.6	23	389.1	11.1	20	408.7	11.7	24	409.1	15.8	
48	21	421.3	18.1	22	475.8	20.5	21	447.1	13.7	22	407.6	12.6	20	423.9	12.1	24	427.5	17.2	
52	21	435.6	19.1	22	494.3	21.8	21	460.4	14.9	22	426.8	14.4	20	435.7	13.2	24	440.7	17.7	

Analysis of Interim Sacrifice Body Weight Data

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

		<i>Dose ($\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$)</i>																	
		<i>0</i>			<i>2.5</i>			<i>25</i>			<i>250</i>			<i>2500</i>			<i>25000</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>	<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	22	84.5	2.5	22	82.9	2.2	20	85.2	2.5	24	80.8	2.3	20	82.8	2.4	22	79.9	1.4	
8	22	297.8	7.1	22	299.0	6.9	20	296.3	7.4	24	288.0	6.7	20	296.4	7.7	21	290.4	5.1	
12	22	424.2	8.8	22	429.1	7.9	20	429.1	9.8	24	415.5	7.5	20	425.7	10.7	21	416.6	8.3	
16	22	494.4	9.8	22	504.7	9.1	20	500.1	11.2	24	490.3	8.5	20	496.0	11.5	21	484.1	9.3	
20	22	540.1	10.5	22	553.9	10.6	19	553.4	13.1	24	540.8	10.0	20	542.0	13.1	21	531.7	10.5	
24	22	578.1	12.1	22	589.6	11.5	19	586.3	14.3	24	576.3	11.5	20	579.4	14.5	21	567.8	11.7	
28	21	604.4	13.4	22	620.6	12.3	19	612.4	15.3	24	607.3	12.3	20	610.2	16.2	21	595.5	12.8	
32	21	627.1	14.0	22	643.4	13.1	19	636.5	15.8	24	632.7	12.5	20	635.4	18.2	21	619.8	13.5	
36	21	645.1	15.0	22	666.6	14.1	19	653.1	17.1	24	653.1	13.1	20	655.7	19.2	21	638.7	14.5	
40	20	664.2	17.2	22	690.0	16.0	19	673.2	18.1	24	674.0	13.5	19	674.8	20.6	21	658.6	15.4	
44	19	688.0	16.0	22	707.0	17.1	19	688.9	18.9	24	691.0	14.4	19	693.0	21.1	21	675.5	17.0	
48	19	701.6	17.6	22	723.7	19.5	18	714.6	19.9	24	711.8	15.3	18	705.6	24.3	21	693.3	17.4	
52	18	720.2	19.5	22	742.1	20.6	18	729.3	21.5	24	732.1	15.7	18	724.3	26.0	21	713.5	18.6	

Analysis of Interim Sacrifice Body Weight Data

Table 9. ANOVA Results for Body Weight Interim Sacrifice Female 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	129	3.097	0.011
Week	12	1527	1138.354	<.001
Dose*Week	60	1527	0.564	0.997

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

<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																									
		<i>0</i>				<i>2.5</i>				<i>25</i>				<i>250</i>				<i>2500</i>				<i>25000</i>			
<i>Week</i>	<i>Mean</i>	<i>SE</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>		
4	75.6	1.7	0.306	76.6	1.7	101.3	0.994	75.7	1.7	100.0	1.000	73.6	1.6	97.3	0.849	73.0	1.8	96.5	0.727	75.3	1.6	99.6	1.000		
8	195.7	4.2	0.502	203.4	4.3	103.9	0.566	204.9	4.3	104.7	0.396	195.8	4.1	100.1	1.000	196.0	4.5	100.1	1.000	197.3	4.1	100.8	0.999		
12	264.2	5.6	0.132	277.3	5.7	104.9	0.339	277.9	5.7	105.2	0.298	265.5	5.5	100.5	1.000	261.6	6.0	99.0	0.998	262.0	5.5	99.2	0.999		
16	297.9	6.9	0.067	314.3	7.0	105.5	0.316	316.6	7.0	106.3	0.204	298.8	6.7	100.3	1.000	293.4	7.3	98.5	0.989	292.9	6.7	98.3	0.979		
20	317.2	8.3	0.063	342.1	8.4	107.9	0.135	345.0	8.4	108.8	0.078	316.5	8.1	99.8	1.000	311.2	8.9	98.1	0.984	315.5	8.1	99.5	1.000		
24	335.6	9.8	0.068	363.2	9.8	108.2	0.173	362.2	9.8	107.9	0.199	331.3	9.4	98.7	0.998	330.7	10.3	98.5	0.997	331.6	9.4	98.8	0.999		
28	349.1	10.7	0.121	382.4	10.8	109.5	0.111	380.3	10.8	108.9	0.151	343.6	10.3	98.4	0.996	345.7	11.3	99.0	1.000	350.9	10.3	100.5	1.000		
32	365.4	12.0	0.119	402.7	12.1	110.2	0.111	394.9	12.1	108.1	0.285	359.7	11.6	98.4	0.997	361.8	12.7	99.0	1.000	365.8	11.6	100.1	1.000		
36	379.2	13.1	0.101	422.4	13.2	111.4	0.080	409.8	13.2	108.1	0.330	374.4	12.6	98.7	0.999	376.1	13.8	99.2	1.000	378.3	12.6	99.8	1.000		
40	391.9	13.6	0.173	439.3	13.7	112.1	0.058	422.2	13.7	107.7	0.376	383.5	13.2	97.9	0.990	394.3	14.3	100.6	1.000	395.8	13.1	101.0	1.000		
44	405.6	14.8	0.191	455.2	14.8	112.3	0.071	433.9	14.8	107.0	0.519	395.7	14.3	97.6	0.986	408.7	15.5	100.8	1.000	409.1	14.2	100.9	1.000		
48	420.9	16.1	0.232	475.8	16.1	113.0	0.065	449.5	16.1	106.8	0.591	413.0	15.6	98.1	0.997	423.9	16.8	100.7	1.000	427.5	15.4	101.6	0.998		
52	435.2	17.2	0.209	494.3	17.1	113.6	0.062	462.8	17.3	106.4	0.681	432.0	16.7	99.3	1.000	435.7	18.0	100.1	1.000	440.7	16.4	101.3	1.000		

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

Analysis of Interim Sacrifice Body Weight Data

Table 11. ANOVA Results for Body Weight Interim 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	124	0.504	0.773
Week	12	1444	1488.563	<.001
Dose*Week	60	1444	0.199	1.000

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

<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>																							
<i>0</i>		<i>2.5</i>				<i>25</i>				<i>250</i>				<i>2500</i>				<i>25000</i>					
<i>Week</i>	<i>Mean</i>	<i>SE</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>
4	84.5	2.2	0.143	82.9	2.2	98.1	0.983	85.2	2.3	100.8	1.000	80.8	2.1	95.7	0.636	82.8	2.3	98.0	0.981	79.9	2.2	94.6	0.452
8	297.8	6.8	0.341	299.0	6.8	100.4	1.000	296.3	7.1	99.5	1.000	288.0	6.5	96.7	0.747	296.4	7.1	99.5	1.000	290.1	6.8	97.4	0.888
12	424.2	8.7	0.385	429.1	8.7	101.2	0.994	429.1	9.1	101.2	0.994	415.5	8.3	97.9	0.924	425.7	9.1	100.4	1.000	416.2	8.8	98.1	0.951
16	494.4	9.7	0.276	504.7	9.7	102.1	0.915	500.1	10.2	101.1	0.994	490.3	9.3	99.2	0.998	496.0	10.2	100.3	1.000	483.7	9.8	97.8	0.902
20	540.1	11.1	0.344	553.9	11.1	102.6	0.846	549.5	11.6	101.7	0.967	540.8	10.6	100.1	1.000	542.0	11.6	100.4	1.000	531.3	11.2	98.4	0.973
24	578.1	12.4	0.390	589.6	12.4	102.0	0.948	582.3	13.1	100.7	0.999	576.3	11.8	99.7	1.000	579.4	13.0	100.2	1.000	567.4	12.5	98.1	0.962
28	605.7	13.5	0.450	620.6	13.4	102.5	0.898	608.6	14.2	100.5	1.000	607.3	12.8	100.3	1.000	610.2	14.1	100.7	1.000	595.1	13.6	98.2	0.974
32	628.4	14.3	0.569	643.4	14.2	102.4	0.916	632.8	15.1	100.7	1.000	632.7	13.6	100.7	1.000	635.4	14.9	101.1	0.997	619.4	14.5	98.6	0.991
36	646.3	15.3	0.592	666.6	15.1	103.1	0.812	649.5	16.1	100.5	1.000	653.1	14.5	101.1	0.998	655.7	15.9	101.5	0.992	638.3	15.4	98.8	0.996
40	660.1	16.5	0.678	690.0	16.2	104.5	0.564	669.8	17.3	101.5	0.993	674.0	15.5	102.1	0.961	672.6	17.1	101.9	0.979	658.2	16.5	99.7	1.000
44	676.2	17.3	0.738	707.0	16.8	104.5	0.577	685.7	18.0	101.4	0.995	691.0	16.1	102.2	0.957	690.9	17.8	102.2	0.966	675.1	17.2	99.8	1.000
48	690.2	18.9	0.818	723.7	18.1	104.9	0.573	706.4	19.5	102.3	0.965	711.8	17.4	103.1	0.869	705.2	19.4	102.2	0.974	693.0	18.5	100.4	1.000
52	705.7	20.3	0.968	742.1	19.3	105.2	0.559	721.4	20.9	102.2	0.977	732.1	18.5	103.7	0.799	723.9	20.8	102.6	0.957	713.1	19.7	101.1	0.999

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

Analysis of Interim Sacrifice Body Weight Data

c) *EE₂ Treatments Continuous Dose*

**Table 13. Summary Statistics for Interim 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	23	75.6	1.3	26	74.8	1.6	26	80.7	1.9	
8	23	195.7	5.3	26	201.3	4.4	26	209.2	3.8	
12	22	268.0	6.0	26	272.6	6.7	26	262.4	4.9	
16	22	302.0	7.5	26	307.9	7.4	26	291.1	5.3	
20	22	321.7	8.3	26	332.5	8.2	26	312.1	6.5	
24	22	340.4	9.9	26	352.0	8.9	26	329.5	7.9	
28	22	353.8	10.5	26	365.0	9.1	26	348.1	8.5	
32	22	370.1	12.9	26	383.9	10.0	26	366.6	9.5	
36	22	383.8	13.9	26	397.9	10.4	26	384.3	10.5	
40	22	396.2	14.6	25	417.3	11.1	26	397.4	10.5	
44	22	409.7	15.6	25	433.7	11.2	26	411.7	10.9	
48	21	421.3	18.1	24	448.7	12.9	26	426.9	11.6	
52	21	435.6	19.1	24	468.1	13.6	26	440.3	12.3	

Analysis of Interim Sacrifice Body Weight Data

**Table 14. Summary Statistics for Interim Sacrifice
Male 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	22	84.5	2.5	26	83.5	2.1	26	88.3	2.1	
8	22	297.8	7.1	26	297.8	7.0	26	304.3	5.4	
12	22	424.2	8.8	26	431.2	8.8	26	437.2	6.2	
16	22	494.4	9.8	26	503.7	10.2	26	505.4	7.9	
20	22	540.1	10.5	25	551.4	12.3	24	550.1	9.9	
24	22	578.1	12.1	25	588.4	13.3	26	584.0	9.2	
28	21	604.4	13.4	25	613.2	13.6	26	611.4	10.0	
32	21	627.1	14.0	25	635.9	14.3	26	634.3	10.3	
36	21	645.1	15.0	25	660.2	15.3	25	651.8	11.7	
40	20	664.2	17.2	24	680.8	16.5	25	672.7	12.6	
44	19	688.0	16.0	25	697.2	17.4	25	686.7	13.3	
48	19	701.6	17.6	24	712.4	18.9	23	714.8	14.2	
52	18	720.2	19.5	22	729.7	21.4	23	723.7	15.7	

Analysis of Interim Sacrifice Body Weight Data

**Table 15. ANOVA Results for Body Weight Interim Sacrifice
Female Ethinyl Estradiol 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	2	72	1.485	0.233
Week	12	845	531.786	<.001
Dose*Week	24	845	1.899	0.005

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

<i>Week</i>	<i>Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)</i>										
	<i>0</i>			<i>0.05</i>				<i>0.5</i>			
	<i>Mean</i>	<i>SE</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	
4	75.6	1.7	74.8	1.6	98.9	0.916	80.7	1.6	106.7	0.060	
8	195.7	4.7	201.3	4.4	102.9	0.590	209.2	4.4	106.9	0.066	
12	264.3	6.2	272.6	5.8	103.1	0.512	262.4	5.8	99.3	0.963	
16	298.3	7.0	307.8	6.6	103.2	0.506	291.1	6.6	97.6	0.672	
20	317.8	8.0	332.5	7.5	104.6	0.303	312.1	7.5	98.2	0.819	
24	336.4	9.2	352.0	8.6	104.7	0.356	329.5	8.6	98.0	0.808	
28	350.0	9.8	365.0	9.1	104.3	0.423	348.1	9.1	99.5	0.985	
32	366.2	11.2	383.9	10.4	104.9	0.403	366.6	10.4	100.1	0.999	
36	380.0	12.1	397.9	11.2	104.7	0.447	384.3	11.2	101.1	0.951	
40	392.7	12.5	417.6	11.6	106.3	0.249	397.4	11.6	101.2	0.946	
44	406.4	13.1	434.0	12.1	106.8	0.213	411.7	12.1	101.3	0.937	
48	421.8	14.6	449.7	13.5	106.6	0.274	426.9	13.4	101.2	0.952	
52	436.0	15.5	469.1	14.4	107.6	0.205	440.3	14.1	101.0	0.970	

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

Analysis of Interim Sacrifice Body Weight Data

Table 17. ANOVA Results for Body Weight Interim 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	71	0.466	0.629
Week	12	812	927.172	<.001
Dose*Week	24	812	0.272	0.999

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

<i>Week</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>Mean</i>	<i>SE</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>P value</i>
4	84.5	2.4	83.6	2.2	98.9	0.942	88.3	2.2	104.6	0.382
8	297.8	6.9	298.0	6.3	100.1	1.000	304.4	6.3	102.2	0.702
12	424.2	8.5	431.5	7.8	101.7	0.748	437.3	7.8	103.1	0.414
16	494.4	9.9	504.0	9.1	101.9	0.698	505.5	9.1	102.2	0.622
20	540.1	11.3	553.9	10.5	102.6	0.572	549.6	10.5	101.8	0.762
24	578.1	12.2	590.9	11.3	102.2	0.658	583.0	11.1	100.9	0.936
28	605.7	12.9	615.7	12.0	101.7	0.792	610.4	11.8	100.8	0.948
32	628.3	13.6	638.5	12.5	101.6	0.805	633.3	12.3	100.8	0.947
36	646.3	14.8	662.9	13.6	102.6	0.619	651.5	13.3	100.8	0.950
40	660.0	16.0	680.0	14.7	103.0	0.557	672.3	14.4	101.9	0.794
44	676.3	16.5	697.6	15.0	103.1	0.534	686.4	14.9	101.5	0.862
48	690.4	17.8	715.0	16.0	103.6	0.484	707.2	15.9	102.4	0.704
52	705.5	19.7	733.2	17.7	103.9	0.473	722.4	17.4	102.4	0.746

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

B. Figures

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

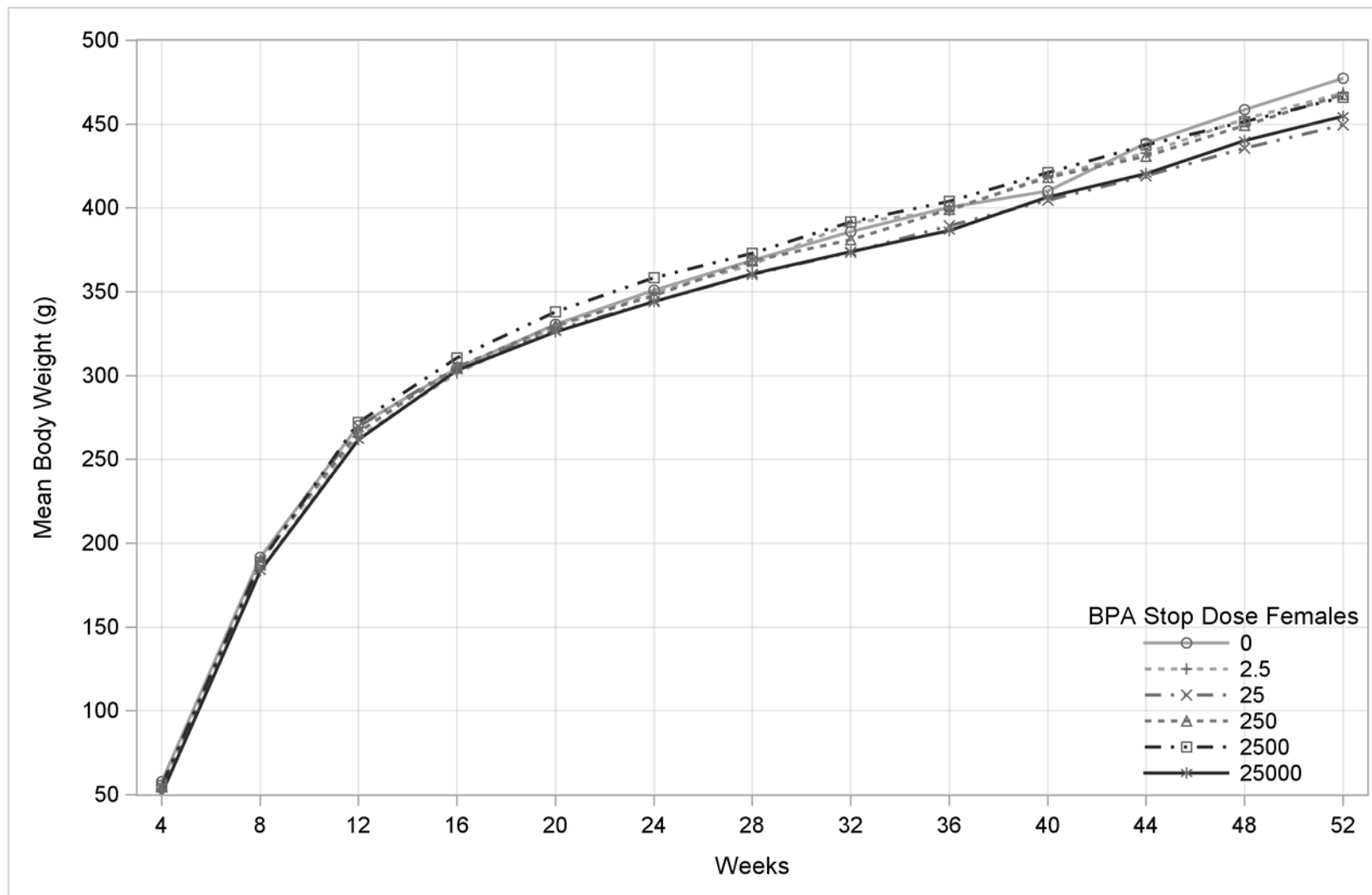


Figure 2. Body Weight (g) for Interim Sacrifice Males in the BPA Stop Dose Arm

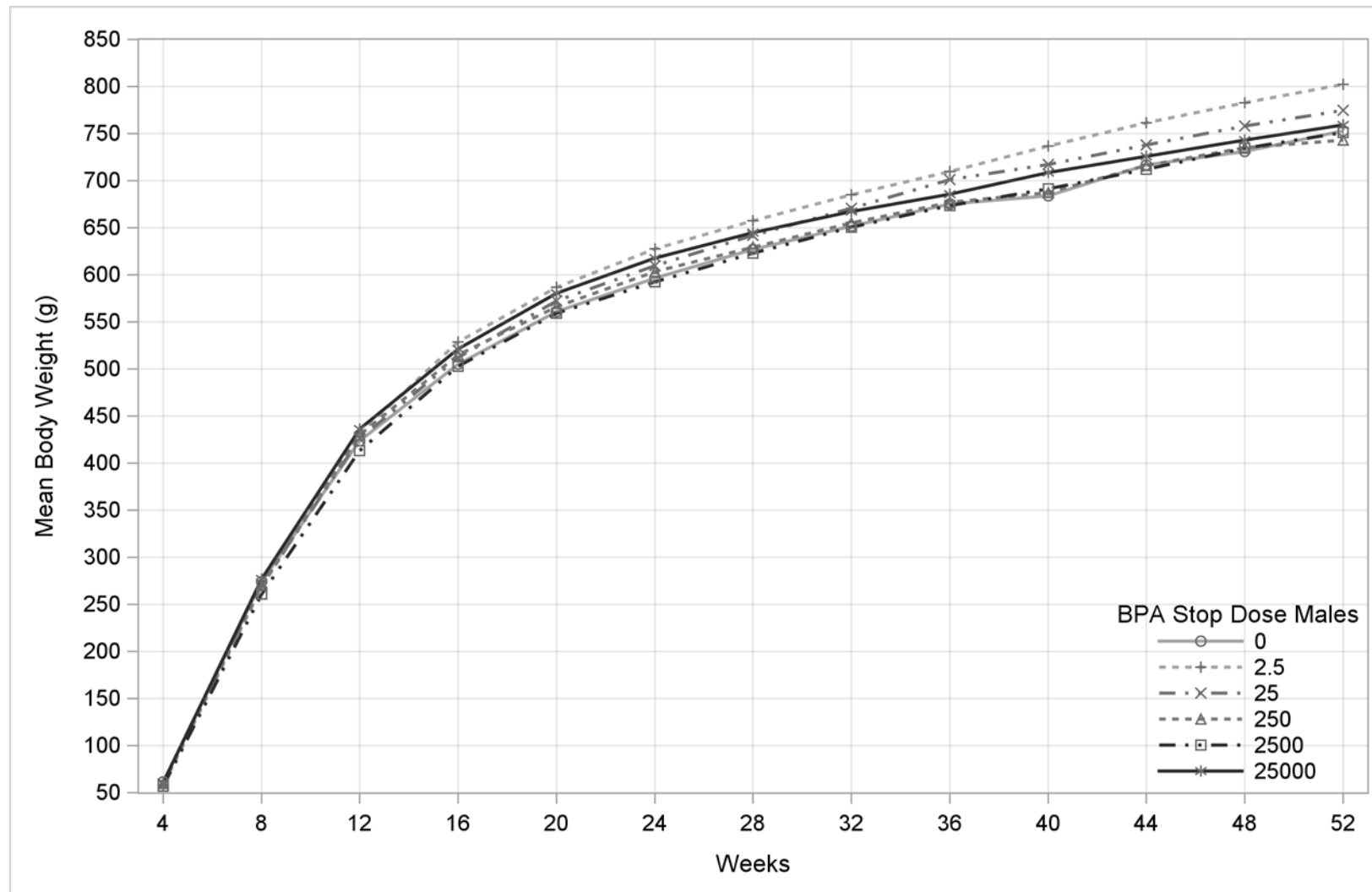


Figure 3. Body Weight (g) for Interim Sacrifice Females in the BPA Continuous Dose Arm

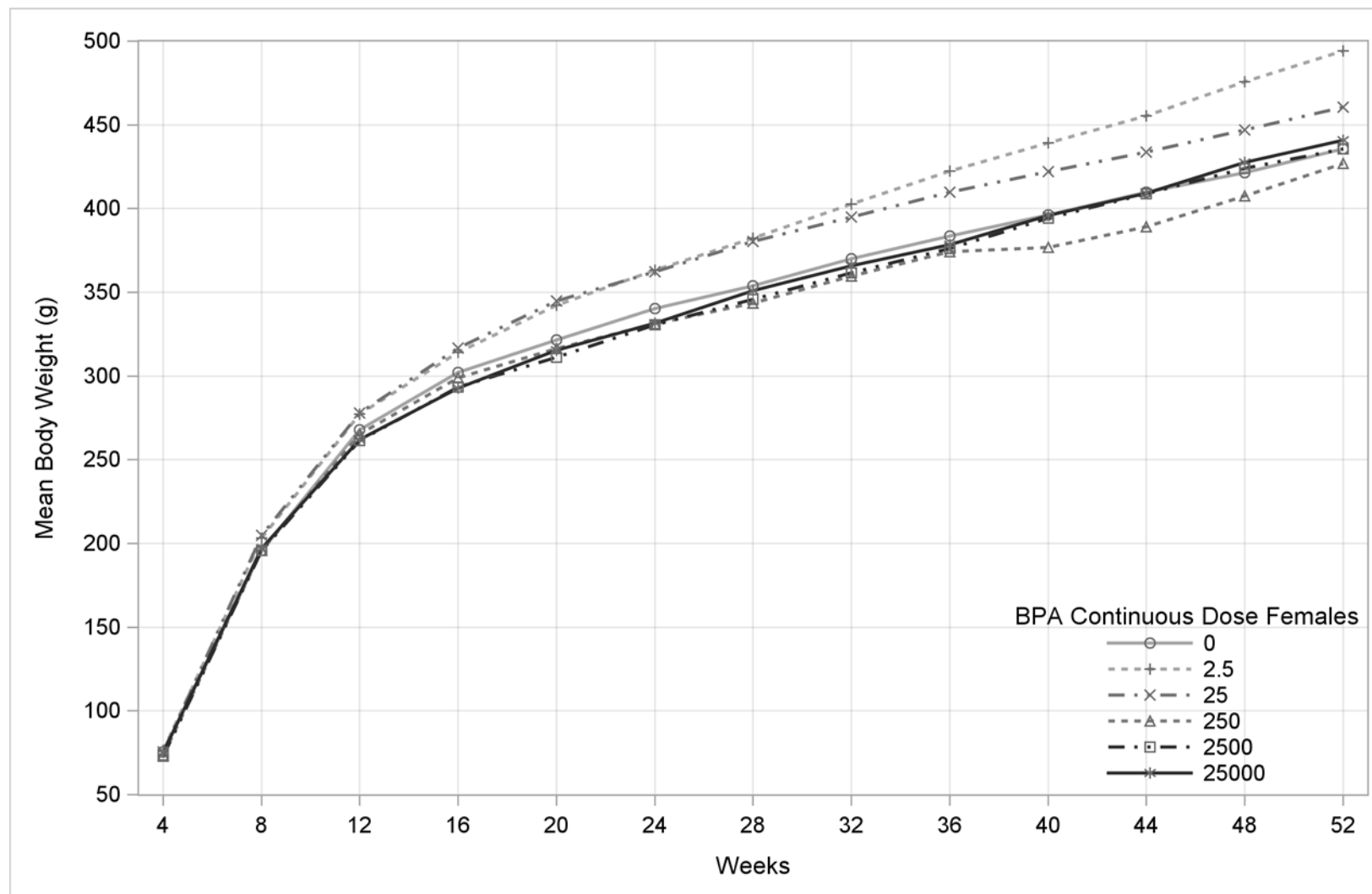


Figure 4. Body Weight (g) for Interim Sacrifice Males in the BPA Continuous Dose Arm

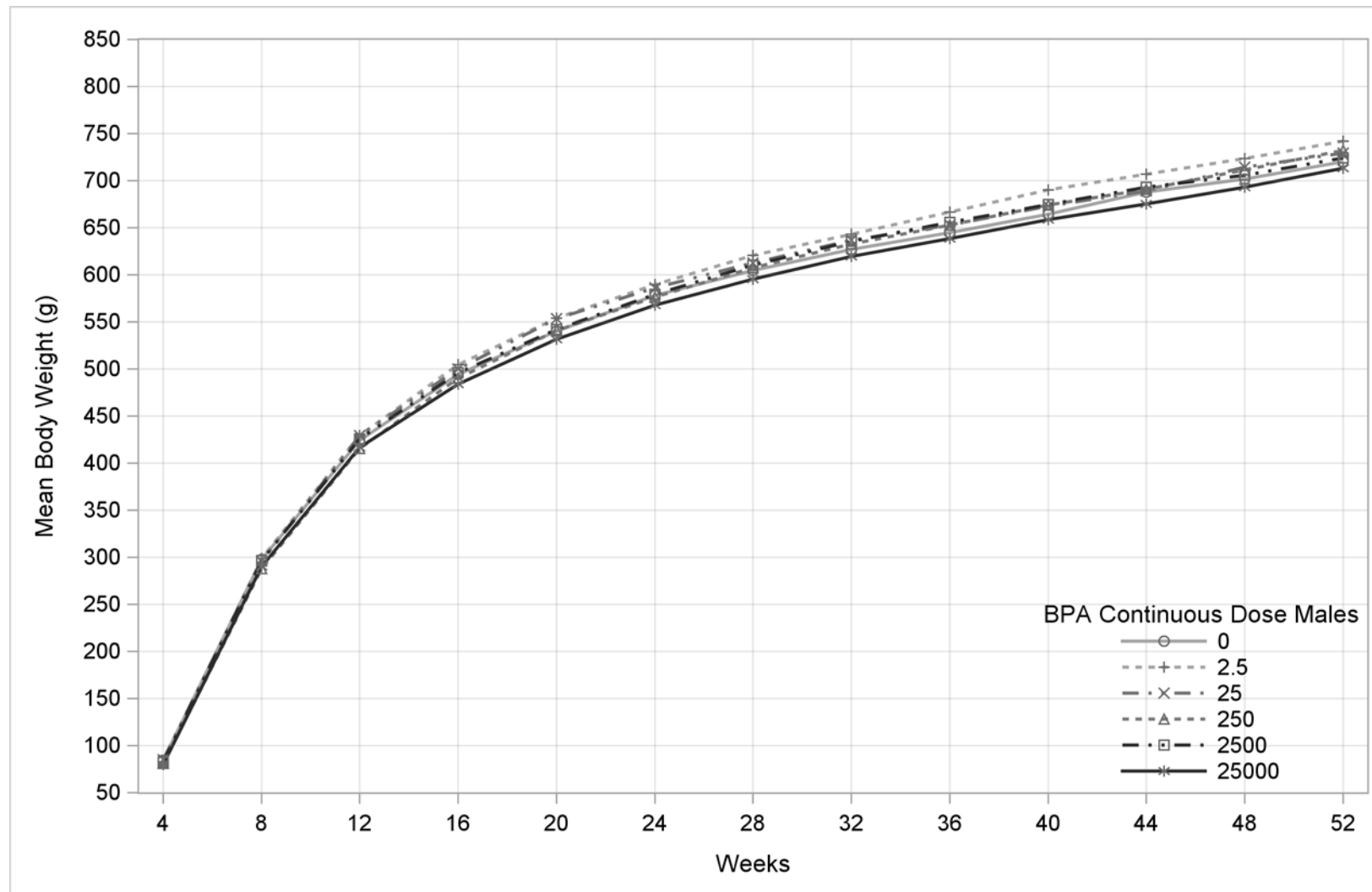


Figure 5. Body Weight (g) for Interim Sacrifice Females EE₂ Continuous Dose

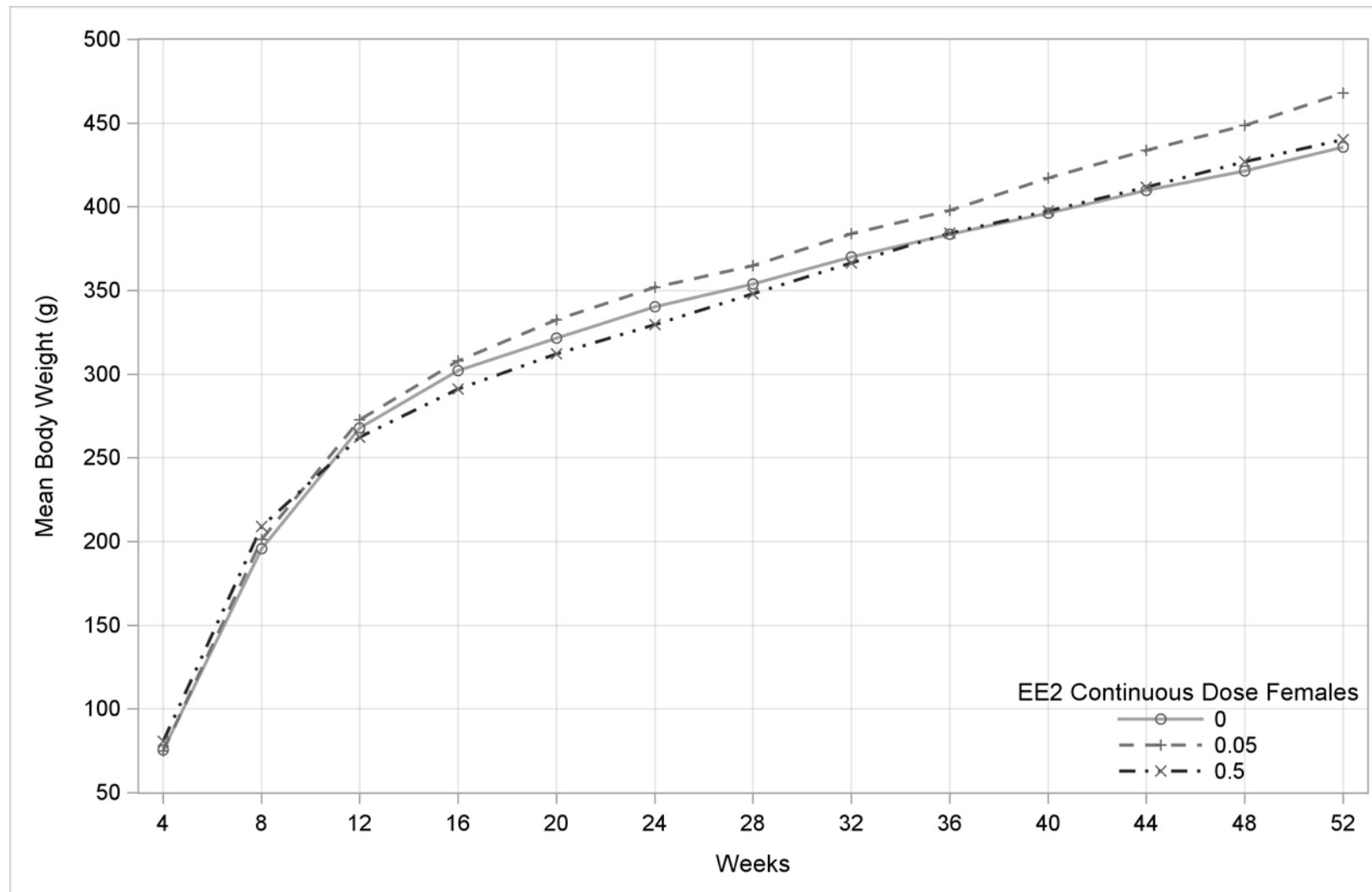
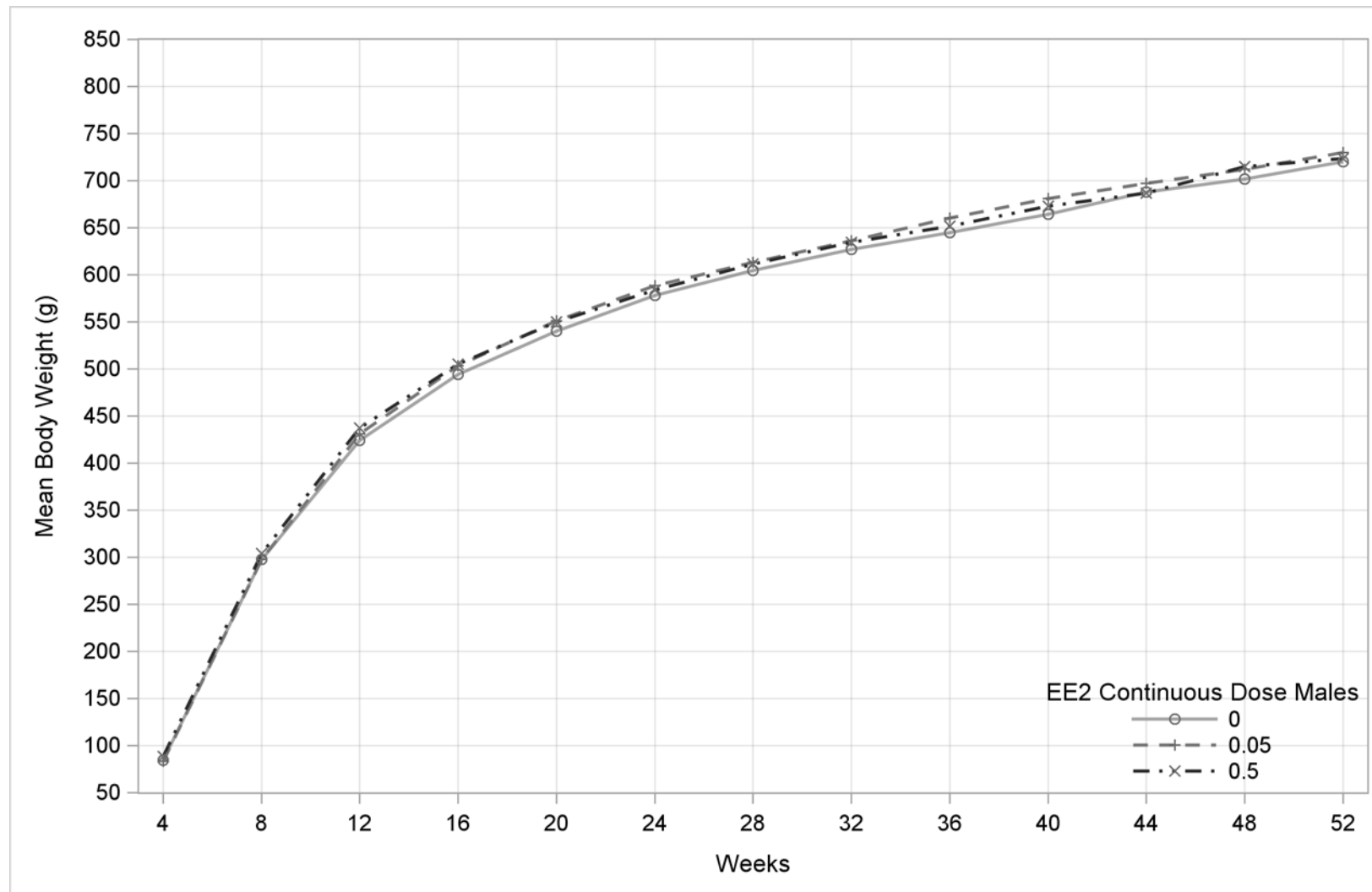


Figure 6. Body Weight (g) for Interim Sacrifice Males EE₂ Continuous Dose



Analysis of Interim Sacrifice Body Weight Data

C. Outliers**Table 1. Outliers¹ for Interim Sacrifice Body Weight Bisphenol-A Stop-Dose ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)**

<i>Sex</i>	<i>UIN</i>	<i>Dose</i>	<i>Week</i>	<i>Weight (g)</i>	<i>Difference (g)²</i>
F	23000535642	0	16	286.0	-41.8
	23000536011	0	16	389.1	48.1
M	23000528317	2.5	48	692.8	-35.9
	23000534332	25	36	763.2	76.0
	23000530811	250	52	734.2	-51.3

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 35 with graphical confirmation for week 4.

Table 2. Outliers¹ for Interim Sacrifice Body Weight Ethinyl Estradiol ($\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$)

<i>Sex</i>	<i>UIN</i>	<i>Dose</i>	<i>Week</i>	<i>Weight (g)</i>	<i>Difference (g)²</i>
M	23000533518	0.05	40	545.2	-66.6
	23000530450	0.5	20	519.0	-41.5
	23000530735	0.5	20	480.3	-41.7
	23000534809	0.5	48	577.1	-38.9

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 35 (g) with graphical confirmation for week 4 due to rapid early post-weaning growth.

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.