

Statistical Report

Project #: E2190.01
Project Title: 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 1 (PND 1); Continuous
and Stop Dose (PND 21) Exposures
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Task: Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)
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Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

1. Objectives

1.1 Project Objectives

The goal of this study is to study the long term toxicity of orally administered Bisphenol-A (BPA) over a broad dose range.

1.2 Analysis Objectives

The objective of this analysis is to determine the effects on histopathology of a broad range of continuous and stop doses of BPA after one year. Statistical analyses of data from continuous doses of the reference estrogen EE₂ are also presented.

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 (2.5, 25, 250, 2500, and 25000 µg/kg) for each study dosing arm, and EE₂ daily dose groups (0.05 and 0.50 µg/kg) 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.

3. Statistical Methods

Statistical analyses were performed separately for the BPA study arms, stop dose and continuous dose, and for the EE₂ continuous dose.

For neoplasm and non-neoplasm incidence, the Cochran-Armitage test was used to test for linear dose trend, with Fisher's exact test to compare dosed groups to the vehicle control. This combination of tests is referred to as CAFE.

In addition, non-neoplastic lesion severity is available for many of the lesions found. Therefore, the Jonckheere-Terpstra test (Jonckheere (1954) and Terpstra (1952)) was run to test for monotonic dose trend, followed by Shirley's test (Shirley, 1977 and Williams, 1986) to compare treated groups to controls. This combination of tests will be referred to as JT/SW. JT/SW presumes a monotonic dose response. Part of the purpose of this study is to consider potential

low-dose effects, especially in the low BPA analysis. JT/SW is blind to this effect. Therefore, the nonparametric relative effects method [RTE] (Brunner, Domhof, Langer, 2002) was used to test for non-monotonic effects. This method can account for severity and does allow for trend tests and contrasts. The RTE test (as well as JT/SW) can be very sensitive to small differences in severity.

Lesions with an incidence of two or more in any treatment group were included in each analysis. The tests for the comparisons to vehicle are one-sided while the trend tests are two-sided. No adjustments are made for multiplicity.

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.

4. Results

Tables are included in Appendix A1. Generally, simple incidence refers to all animals for which the given tissue was microscopically examined, terminal incidence refers to animals which survived to scheduled sacrifice, time-to-first indicates the number of study days of the earliest observance of the lesion, and severity profile summarizes the number of animals with minimal, mild, moderate, and marked lesion severity.

For females, there were 195 lesions assessed in 21 tissues examined. For males, 169 lesions were assessed in 23 tissues examined.

The results of CAFE analysis of lesion incidence and RTE analysis are discussed below. Results of JT/SW are presented in the tables for reference, but are not discussed.

4.1 *BPA Treatments Stop Dose Arm*

Results of the CAFE analysis of neoplasms for the comparison of BPA to vehicle control for the stop dose arm are given in Tables 1 (females) and 2 (males). There was no statistically different incidence of neoplasms for any BPA group for either females or males.

Results of the analysis of non-neoplasms for the comparison of BPA to vehicle control for the stop-dose arm are given in Tables 7 (females) and 8 (males). For females, there was a significantly greater incidence of liver mononuclear cell infiltration for the 2.5 $\mu\text{g}/\text{kg}$ BPA group ($p=0.012$) and the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p=0.048$) compared to the vehicle control group. There was a significantly greater incidence of ovary follicle cysts in the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p<0.001$) compared to controls. In addition, the RTE test for differences in severity was

significant for adrenal cortex cystic degeneration at 250 $\mu\text{g}/\text{kg}$ ($p=0.037$), pituitary gland angiectasis at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.015$), thyroid gland hyperplasia c-cell at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.024$), uterus lumen dilation at 250 $\mu\text{g}/\text{kg}$ ($p=0.045$), uterus endometrium cystic hyperplasia at 25,000 $\mu\text{g}/\text{kg}$ ($p=0.030$), uterus squamous metaplasia at 25,000 $\mu\text{g}/\text{kg}$ ($p=0.005$), and thymus atrophy at 25 $\mu\text{g}/\text{kg}$ ($p=0.024$).

For males, there was a significantly greater incidence of spleen pigmentation for the 250 $\mu\text{g}/\text{kg}$ BPA group ($p=0.012$). The RTE test for differences in severity was significant for heart cardiomyopathy at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.027$) and 25 $\mu\text{g}/\text{kg}$ ($p=0.006$), epididymis exfoliated germ cell at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.034$), and bone marrow myeloid cell hyperplasia at 25 $\mu\text{g}/\text{kg}$ ($p=0.020$).

4.2 BPA Treatments Continuous Dose Arm

Results of the CAFE analysis of neoplasms for the comparison of BPA to vehicle control for the continuous dose arm are given in Tables 3 (females) and 4 (males). There was no statistically different incidence of neoplasms for any BPA group for either females or males. There was a significant dose trend for uterus stromal polyp for females ($p=0.037$).

Results of the analysis of non-neoplasms for the comparison of BPA to vehicle control for the continuous dose arm are given in Tables 9 (females) and 10 (males). For females, there was a significantly greater incidence of uterus apoptosis for the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p=0.022$) compared to the vehicle control group. There was a significantly greater incidence of kidney renal tubule cysts in the 2.5 $\mu\text{g}/\text{kg}$ BPA group ($p=0.004$) compared to controls. There was an additional dose trend for ovary corpus luteum cysts ($p=0.047$), ovary corpus luteum depletion ($p=0.032$), ovary interstitial cell hypertrophy ($p=0.030$), uterus estrus ($p=0.014$), uterus squamous metaplasia ($p=0.037$), vagina estrus ($p=0.003$), vagina epithelium hyperplasia ($p=0.008$), and kidney mineralization ($p=0.017$). In addition, the RTE test for differences in severity was significant for pancreas cellular lymphocyte infiltration at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.007$), uterus endometrium hyperplasia at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.042$) and 250 $\mu\text{g}/\text{kg}$ ($p=0.049$), vagina epithelium hyperplasia at 25,000 $\mu\text{g}/\text{kg}$ ($p=0.030$), mammary gland atypical focus at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.017$), mammary gland dilatation duct at 25 $\mu\text{g}/\text{kg}$ ($p=0.010$), kidney mineralization at 25,000 $\mu\text{g}/\text{kg}$ ($p=0.025$), and kidney nephropathy at 25 $\mu\text{g}/\text{kg}$ ($p=0.036$) and at 2500 $\mu\text{g}/\text{kg}$ ($p=0.048$).

For males, there was a significantly greater incidence of liver hepatodiaphragmatic nodule for the 2500 $\mu\text{g}/\text{kg}$ BPA group ($p=0.038$), and of liver mononuclear cell infiltration for the 250 $\mu\text{g}/\text{kg}$ BPA group ($p=0.029$) and the 2500 $\mu\text{g}/\text{kg}$ BPA group ($p=0.023$) compared to the vehicle control group. There was a significantly greater incidence of epididymis exfoliated germ cells ($p=0.047$) and epididymis cellular lymphocyte infiltration ($p=0.024$) in the 25,000 $\mu\text{g}/\text{kg}$ BPA group compared to controls. There was an additional dose trend for kidney mineralization ($p=0.017$) and for spleen hematopoietic cell proliferation ($p=0.028$). In addition, the RTE test for differences in severity was significant for liver fatty change at 25 $\mu\text{g}/\text{kg}$ ($p=0.012$), liver mononuclear cell infiltration for the 2.5 $\mu\text{g}/\text{kg}$ group ($p=0.034$), adrenal cortex cytoplasmic vacuolization at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.031$), dorsal/lateral lobe prostate cellular lymphocyte infiltration at 2.5 $\mu\text{g}/\text{kg}$ ($p=0.025$), dorsal/lateral lobe prostate suppurative inflammation at 2.5 $\mu\text{g}/\text{kg}$

($p=0.025$), 250 $\mu\text{g}/\text{kg}$ ($p=0.048$), and 2500 $\mu\text{g}/\text{kg}$ ($p=0.022$), and spleen hematopoietic cell proliferation at 25,000 $\mu\text{g}/\text{kg}$ ($p=0.013$). There was a significant severity trend, based on the RTE test, for liver cytoplasmic vacuolization ($p=0.046$).

4.3 *EE₂ Treatments Continuous Dose Arm*

Results of the CAFE analysis of neoplasms for the comparison of EE₂ to vehicle control for the continuous dose arm are given in Tables 5 (females) and 6 (males). There was no statistically different incidence of neoplasms for any EE₂ group for either females or males.

Results of the analysis of non-neoplasms for the comparison of EE₂ to vehicle control for the continuous dose arm are given in Tables 11 (females) and 12 (males). For females, based on the CAFE tests, there was a significantly greater incidence of heart cardiomyopathy ($p=0.015$), ovary atrophy ($p<0.001$), ovary follicle cyst ($p<0.001$), ovary corpus luteum depletion ($p<0.001$), ovary interstitial cell hypertrophy ($p<0.001$), uterus apoptosis ($p<0.001$), uterus estrus ($p<0.001$), uterus cystic endometrium hyperplasia ($p=0.021$), uterus squamous metaplasia ($p<0.001$), vagina estrus ($p<0.001$), vagina epithelium hyperplasia ($p<0.001$), mammary gland duct dilation ($p<0.001$), mammary gland lobular hyperplasia ($p<0.001$), and kidney nephropathy ($p=0.025$) for the 0.5 $\mu\text{g}/\text{kg}$ EE₂ group compared to the vehicle control group. There was a significantly greater incidence of kidney renal tubule cysts in the 0.05 $\mu\text{g}/\text{kg}$ EE₂ group ($p=0.034$) compared to controls. There was a significant dose trend for pituitary gland angiectasis at ($p=0.034$), for ovary bursa cyst ($p=0.027$), for ovary follicle cyst ($p<0.001$), for vagina epithelium mucification ($p=0.048$), and for mammary gland galactocele ($p=0.012$). In addition, the RTE test for differences in severity was significant for pituitary gland angiectasis at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.025$), pituitary gland pars distalis hyperplasia at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.003$), vagina epithelium mucification at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.027$), spleen pigmentation at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.001$), and kidney mineralization at 0.05 $\mu\text{g}/\text{kg}$ ($p=0.030$).

For males, there was a significantly greater incidence of liver mononuclear cell infiltration for the 0.05 $\mu\text{g}/\text{kg}$ EE₂ group ($p=0.049$) compared to the vehicle control group. There was an additional dose trend for liver fatty change ($p=0.028$). In addition, the RTE test for differences in severity was significant for liver fatty change at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.019$) and epididymis cellular lymphocyte infiltration at 0.5 $\mu\text{g}/\text{kg}$ ($p=0.044$).

4.4 *Sensitivity Analysis*

The results of the sensitivity analysis, excluding animals housed in the same room as animals exposed to BPA 250,000 $\mu\text{g}/\text{kg}$ bw/day high dose, produced results highly similar to the full analysis. There were a few significant results observed in the full analysis which were not observed in the sensitivity analysis, presumably due to the lesser statistical power of the data subset. There were two significant (CAFE) lesion incidence results in the sensitivity analysis which were not observed in the full analysis. A significant ($p=0.048$) difference in uterus squamous metaplasia for continuous dose females in the 25,000 $\mu\text{g}/\text{kg}$ BPA group (5/20) compared to controls (0/15) based on CAFE; a nonsignificant difference for the full analysis where five of 24 animals had the lesion in the BPA group compared to one of 23 in the control

group. A significant ($p=0.025$) difference in dorsal/lateral lobe prostate cellular lymphocyte infiltration (9/16) for continuous dose males in the 2.5 $\mu\text{g}/\text{kg}$ BPA group compared to controls (3/17) based on CAFE; a nonsignificant difference for the full analysis where ten of 22 animals had the lesion in the BPA group compared to four of 22 for the control group.

5. Conclusions

There was no neoplasm incidence that was significantly greater than control for any stop-dose BPA, continuous dose BPA, or continuous dose EE₂ group for either females or males. There was a significant dose trend for uterus stromal polyp for females ($p=0.037$). The incidence for the control group was 1/23 (4.3%) compared to 3/20 (15.0%) for the 2500 $\mu\text{g}/\text{kg}$ BPA group and 3/24 (12.5%) for the 25,000 $\mu\text{g}/\text{kg}$ BPA group.

For stop dose females, there was a significantly greater incidence of liver mononuclear cell infiltration for the 2.5 $\mu\text{g}/\text{kg}$ BPA group ($p=0.012$) and the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p=0.048$) compared to the vehicle control group. There was a significantly greater incidence of ovary follicle cysts in the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p<0.001$) compared to controls. For continuous dose females, there was a significantly greater incidence of uterus apoptosis for the 25,000 $\mu\text{g}/\text{kg}$ BPA group ($p=0.022$) compared to the vehicle control group. There was a significantly greater incidence of kidney renal tubule cysts in the 2.5 $\mu\text{g}/\text{kg}$ BPA group ($p=0.004$) compared to controls.

For stop dose males, there was a significantly greater incidence of spleen pigmentation for the 250 $\mu\text{g}/\text{kg}$ BPA group. For continuous dose males, there was a significantly greater incidence of liver mononuclear cell infiltration for the 250 $\mu\text{g}/\text{kg}$ BPA group ($p=0.029$) and the 2500 $\mu\text{g}/\text{kg}$ BPA group ($p=0.023$) compared to the vehicle control group. There was a significantly greater incidence of epididymis exfoliated germ cells ($p=0.047$) and epididymis cellular lymphocyte infiltration ($p=0.024$) in the 25,000 $\mu\text{g}/\text{kg}$ BPA group compared to controls.

For continuous dose EE₂ treated females, there were several non-neoplastic lesions of the ovary, uterus, and vagina with highly significant, greater incidence in the 0.5 $\mu\text{g}/\text{kg}$ EE₂ group compared to the vehicle control group. These include ovary atrophy ($p<0.001$), ovary follicle cyst ($p<0.001$), ovary corpus luteum depletion ($p<0.001$), ovary interstitial cell hypertrophy ($p<0.001$), uterus apoptosis ($p<0.001$), uterus estrus ($p<0.001$), uterus cystic endometrium hyperplasia ($p=0.021$), uterus squamous metaplasia ($p<0.001$), vagina estrus ($p<0.001$), vagina epithelium hyperplasia ($p<0.001$). Ovary atrophy, ovary follicle cyst ($p<0.001$), ovary corpus luteum depletion ($p<0.001$), and ovary interstitial cell hypertrophy ($p<0.001$) have 100% incidence in the 0.5 $\mu\text{g}/\text{kg}$ EE₂. Other lesions with significantly greater incidence for the 0.5 $\mu\text{g}/\text{kg}$ EE₂ group were heart cardiomyopathy ($p=0.015$), mammary gland duct dilation ($p<0.001$), mammary gland lobular hyperplasia ($p<0.001$), and kidney nephropathy ($p=0.025$). Spleen pigmentation showed what could be interpreted as a significantly ($p<0.001$) greater severity for the 0.5 $\mu\text{g}/\text{kg}$ EE₂ group.

For males, there was a significantly greater incidence of liver mononuclear cell infiltration for the 0.05 $\mu\text{g}/\text{kg}$ EE₂ group ($p=0.049$) compared to the vehicle control group.

References

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Appendices

A1 Statistical Tables

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 1. Neoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|-------------|-------------|-------------|-------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Integumentary System | | | | | | | |
| Mammary Gland * Adenocarcinoma or Fibroadenoma | Simple Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/20 (10.0%) |
| | Time-to-First | 363 (T) | 365 (T) | 365 (T) | 363 (T) | 364 (T) | 363 (T) |
| | CAFE P-Value | 0.184N | 0.144N | 0.171N | 0.144N | 0.171N | 0.286N |
| Mammary Gland * Fibroadenoma | Simple Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/20 (10.0%) |
| | Time-to-First | 363 (T) | 365 (T) | 365 (T) | 363 (T) | 364 (T) | 363 (T) |
| | CAFE P-Value | 0.184N | 0.144N | 0.171N | 0.144N | 0.171N | 0.286N |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

| <i>Table 2. Neoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|--|------------------|--------------------------|------------|-----------|------------|-------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| none | | | | | | | |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 3. Neoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|---------------|---------------|--------------|---------------|---------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Genital System | | | | | | | |
| Uterus * Polyp Stromal | Simple Incidence | 1/23 (4.3%) | 0/22 (0.0%) | 1/21 (4.8%) | 0/24 (0.0%) | 3/20 (15.0%) | 3/24 (12.5%) |
| | Terminal Incidence | 1/21 (4.8%) | 0/22 (0.0%) | 1/21 (4.8%) | 0/22 (0.0%) | 3/20 (15.0%) | 3/24 (12.5%) |
| | Time-to-First | 362 (T) | ---- | 360 (T) | ---- | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.037 * | 0.511N | 0.733 | 0.489N | 0.252 | 0.321 |
| Integumentary System | | | | | | | |
| Mammary Gland * Adenocarcinoma or Fibroadenoma | Simple Incidence | 2/23 (8.7%) | 4/22 (18.2%) | 4/22 (18.2%) | 1/24 (4.2%) | 2/20 (10.0%) | 6/24 (25.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/22 (18.2%) | 3/21 (14.3%) | 0/22 (0.0%) | 2/20 (10.0%) | 6/24 (25.0%) |
| | Time-to-First | 361 (T) | 356 (T) | 311 | 256 | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.241 | 0.311 | 0.311 | 0.484N | 0.641 | 0.136 |
| Mammary Gland * Fibroadenoma | Simple Incidence | 2/23 (8.7%) | 3/22 (13.6%) | 3/22 (13.6%) | 1/24 (4.2%) | 2/20 (10.0%) | 6/24 (25.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/22 (13.6%) | 2/21 (9.5%) | 0/22 (0.0%) | 2/20 (10.0%) | 6/24 (25.0%) |
| | Time-to-First | 361 (T) | 356 (T) | 311 | 256 | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.150 | 0.478 | 0.478 | 0.484N | 0.641 | 0.136 |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

| <i>Table 4. Neoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|--------------|--------------|--------------|--------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Alimentary System | | | | | | | |
| Liver * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.282N | 0.244N |
| Pancreas * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.282N | 0.244N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 4. Neoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|--------------|--------------|--------------|--------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Cardiovascular System | | | | | | | |
| Heart * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.268N | 0.244N |
| Endocrine System | | | | | | | |
| Adrenal Cortex * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.268N | 0.244N |
| Parathyroid Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/21 (0.0%) | 0/19 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/21 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/21 (0.0%) | 0/17 (0.0%) | 0/24 (0.0%) | 0/17 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.029N* | 0.256N | 0.282N | 0.223N | 0.282N | 0.256N |
| Pituitary Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.268N | 0.244N |
| Genital System | | | | | | | |
| Prostate, Dorsal/Lateral Lobe * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.268N | 0.244N |
| Hematopoietic System | | | | | | | |
| Bone Marrow * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.296N | 0.244N |
| Spleen * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| Table 4. Neoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm | | | | | | | |
|--|--------------------|--------------------------|--------------|--------------|--------------|--------------|--------------|
| System and Neoplasm | | Treatment (ug/kg) | | | | | |
| Lesion | Statistic | Control | 2.5 | 25 | 250 | 2500 | 25000 |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.296N | 0.244N |
| Integumentary System | | | | | | | |
| Mammary Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/21 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/21 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/17 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.256N | 0.268N | 0.223N | 0.282N | 0.244N |
| Urinary System | | | | | | | |
| Kidney * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.282N | 0.244N |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

| Table 5. Neoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm | | | | |
|--|--------------------|--------------------------|---------------|---------------|
| System and Neoplasm | | Treatment (ug/kg) | | |
| Lesion | Statistic | Control | 0.05 | 0.50 |
| Integumentary System | | | | |
| Mammary Gland * Adenocarcinoma | Simple Incidence | 0/23 (0.0%) | 2/26 (7.7%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/24 (4.2%) | 0/26 (0.0%) |
| | Time-to-First | ---- | 257 | ---- |
| | CAFE P-Value | 0.639N | 0.276 | |
| Mammary Gland * Adenocarcinoma or Fibroadenoma | Simple Incidence | 2/23 (8.7%) | 4/26 (15.4%) | 4/26 (15.4%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/24 (12.5%) | 4/26 (15.4%) |
| | Time-to-First | 361 (T) | 257 | 360 (T) |
| | CAFE P-Value | 0.325 | 0.395 | 0.395 |
| Mammary Gland * Fibroadenoma | Simple Incidence | 2/23 (8.7%) | 2/26 (7.7%) | 4/26 (15.4%) |

| <i>Table 5. Neoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|--------------|---------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Terminal Incidence | 2/21 (9.5%) | 2/24 (8.3%) | 4/26 (15.4%) |
| | Time-to-First | 361 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.297 | 0.647N | 0.395 |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

| <i>Table 6. Neoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|--------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Alimentary System | | | | |
| Liver * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Pancreas * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/25 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.088N | 0.205N | 0.214N |
| Cardiovascular System | | | | |
| Heart * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Endocrine System | | | | |
| Adrenal Cortex * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Parathyroid Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Pituitary Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Genital System | | | | |
| Prostate, Dorsal/Lateral Lobe * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |

| <i>Table 6. Neoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|--------------|--------------|
| <i>System and Neoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Hematopoietic System | | | | |
| Bone Marrow * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.086N | 0.205N | 0.205N |
| Spleen * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/25 (0.0%) | 0/25 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.090N | 0.214N | 0.214N |
| Integumentary System | | | | |
| Mammary Gland * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/25 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/22 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.088N | 0.205N | 0.214N |
| Urinary System | | | | |
| Kidney * Lymphoma Malignant | Simple Incidence | 2/22 (9.1%) | 0/26 (0.0%) | 0/25 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | 282 | ---- | ---- |
| | CAFE P-Value | 0.088N | 0.205N | 0.214N |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------|--------------------------|----------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Alimentary System | | | | | | | |
| Liver * Basophilic Focus | Simple Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 2/20 (10.0%) |
| | Time-to-First | ---- | 363 (T) | 363 (T) | 364 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.058 | 0.524 | 0.500 | 0.268 | 0.115 | 0.268 |
| Liver * Eosinophilic Focus | Simple Incidence | 0/20 (0.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 0/20 (0.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 2/20 (10.0%) |
| | Time-to-First | ---- | ---- | 365 (T) | 366 (T) | 365 (T) | 363 (T) |
| | CAFE P-Value | 0.059 | | 0.500 | 0.524 | 0.500 | 0.268 |
| Liver * Fatty Change | Simple Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 0/20 (0.0%) |
| | Time-to-First | 365 (T) | 364 (T) | 364 (T) | 363 (T) | 363 (T) | ---- |
| | CAFE P-Value | 0.302N | 0.537 | 0.500 | 0.203 | 0.756 | 0.476N |
| | Severity Profile | 0 1 0 0 | 0 2 0 0 | 0 0 2 0 | 2 2 0 0 | 1 0 0 0 | --- |
| | JT/SW P-Value | 0.245N | 0.694N | 0.793N | 0.885N | 0.618N | 0.371N |
| | RTE P-Value | 0.264N | 0.312 | 0.198 | 0.087 | 0.485N | 0.274N |
| Liver * Hepatodiaphragmatic Nodule | Simple Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 5/20 (25.0%) |
| | Time-to-First | 363 (T) | 361 (T) | 364 (T) | 363 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.051 | 0.537 | 0.756 | 0.732N | 0.500 | 0.115 |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 4/20 (20.0%) | 2/22 (9.1%) | 4/20 (20.0%) | 3/22 (13.6%) | 3/20 (15.0%) | 8/22 (36.4%) |
| | Terminal Incidence | 4/20 (20.0%) | 2/22 (9.1%) | 4/20 (20.0%) | 3/22 (13.6%) | 3/20 (15.0%) | 7/20 (35.0%) |
| | Time-to-First | 361 (T) | 363 (T) | 364 (T) | 362 (T) | 363 (T) | 255 |
| | CAFE P-Value | 0.095 | 0.286N | 0.653 | 0.444N | 0.500N | 0.204 |
| | Severity Profile | 3 1 0 0 | 0 1 1 0 | 3 1 0 0 | 2 1 0 0 | 3 0 0 0 | 7 1 0 0 |
| | JT/SW P-Value | 0.108 | 0.802 | 0.583 | 0.733 | 0.775 | 0.136 |
| | RTE P-Value | 0.121 | 0.221N | 0.500 | 0.308N | 0.325N | 0.099 |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 2/20 (10.0%) | 10/22 (45.5%) | 7/20 (35.0%) | 7/22 (31.8%) | 2/20 (10.0%) | 8/22 (36.4%) |
| | Terminal Incidence | 2/20 (10.0%) | 10/22 (45.5%) | 7/20 (35.0%) | 7/22 (31.8%) | 2/20 (10.0%) | 8/20 (40.0%) |
| | Time-to-First | 364 (T) | 359 (T) | 363 (T) | 363 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.425 | 0.012 * | 0.064 | 0.088 | 0.698 | 0.048 * |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Severity Profile | 1 1 0 0 | 10 0 0 0 | 7 0 0 0 | 7 0 0 0 | 2 0 0 0 | 8 0 0 0 |
| | JT/SW P-Value | 0.439 | 0.010 ** 1 | 0.031 * 1 | 0.046 * 1 | 0.109 | 0.049 * |
| | RTE P-Value | 0.427 | 0.009 ** | 0.053 | 0.081 | 0.460N | 0.038 * |
| Liver * Tension Lipidosis | Simple Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 1/22 (4.5%) | 4/20 (20.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 1/22 (4.5%) | 4/20 (20.0%) | 4/20 (20.0%) |
| | Time-to-First | 366 (T) | 361 (T) | 365 (T) | 363 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.065 | 0.537 | 0.500 | 0.732N | 0.171 | 0.203 |
| | Severity Profile | 0 1 0 0 | 0 1 1 0 | 0 0 1 1 | 0 1 0 0 | 1 2 1 0 | 2 0 1 1 |
| | JT/SW P-Value | 0.060 | 0.296 | 0.308 | 0.446 | 0.075 | 0.102 |
| | RTE P-Value | 0.060 | 0.330 | 0.281 | 0.482N | 0.083 | 0.098 |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 2/20 (10.0%) | 1/22 (4.5%) | 3/20 (15.0%) | 4/22 (18.2%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 2/20 (10.0%) | 1/22 (4.5%) | 3/20 (15.0%) | 4/22 (18.2%) | 0/20 (0.0%) | 0/20 (0.0%) |
| | Time-to-First | 363 (T) | 359 (T) | 363 (T) | 363 (T) | ---- | ---- |
| | CAFE P-Value | 0.137N | 0.463N | 0.500 | 0.380 | 0.244N | 0.221N |
| | Severity Profile | 2 0 0 0 | 1 0 0 0 | 3 0 0 0 | 3 1 0 0 | --- | --- |
| | JT/SW P-Value | 0.121N | 0.249N | 0.562N | 0.727N | 0.191N | 0.158N |
| | RTE P-Value | 0.116N | 0.257N | 0.279 | 0.169 | 0.105N | 0.137N |
| Pancreas * Degeneration,Acinus | Simple Incidence | 16/20 (80.0%) | 14/22 (63.6%) | 13/20 (65.0%) | 14/22 (63.6%) | 17/20 (85.0%) | 17/22 (77.3%) |
| | Terminal Incidence | 16/20 (80.0%) | 14/22 (63.6%) | 13/20 (65.0%) | 14/22 (63.6%) | 17/20 (85.0%) | 16/20 (80.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 363 (T) | 362 (T) | 362 (T) | 255 |
| | CAFE P-Value | 0.288 | 0.204N | 0.240N | 0.204N | 0.500 | 0.565N |
| | Severity Profile | 1 8 6 1 | 3 7 4 0 | 4 8 1 0 | 4 5 4 1 | 6 7 3 1 | 8 8 1 0 |
| | JT/SW P-Value | 0.120N | 0.047N* 1 | 0.015N* 1 | 0.035N* 1 | 0.069N | 0.023N* |
| | RTE P-Value | 0.108N | 0.041N* | 0.014N* | 0.041N* | 0.183N | 0.020N* |
| Pancreas * Pigmentation | Simple Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 0/22 (0.0%) | 4/20 (20.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 4/20 (20.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 0/22 (0.0%) | 4/20 (20.0%) | 2/20 (10.0%) |
| | Time-to-First | 364 (T) | 365 (T) | 364 (T) | ---- | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.445N | 0.144N | 0.171N | 0.043N* | 0.653 | 0.286N |
| | Severity Profile | 4 0 0 0 | 1 0 0 0 | 1 0 0 0 | --- | 4 0 0 0 | 2 0 0 0 |
| | JT/SW P-Value | 0.410N | 0.063N | 0.062N | 0.007N** 1 | 0.110N | 0.113N |
| | RTE P-Value | 0.402N | 0.033N* | 0.038N* | 0.017N* | 0.500 | 0.082N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------|--------------------------|---------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Cardiovascular System | | | | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 6/20 (30.0%) | 8/22 (36.4%) | 7/20 (35.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 7/22 (31.8%) |
| | Terminal Incidence | 6/20 (30.0%) | 8/22 (36.4%) | 7/20 (35.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 7/20 (35.0%) |
| | Time-to-First | 362 (T) | 364 (T) | 363 (T) | 362 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.457N | 0.457 | 0.500 | 0.582 | 0.634 | 0.582 |
| | Severity Profile | 6 0 0 0 | 8 0 0 0 | 6 1 0 0 | 5 2 0 0 | 6 0 0 0 | 5 2 0 0 |
| | JT/SW P-Value | 0.483 | 0.333 | 0.394 | 0.441 | 0.502 | 0.500 |
| | RTE P-Value | 0.484 | 0.342 | 0.337 | 0.377 | 0.500 | 0.377 |
| Endocrine System | | | | | | | |
| Adrenal Cortex * Degeneration,Cystic | Simple Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/20 (0.0%) |
| | Time-to-First | ---- | 363 (T) | ---- | 364 (T) | ---- | ---- |
| | CAFE P-Value | 0.491N | 0.524 | | 0.268 | | |
| | Severity Profile | --- | 0 0 1 0 | --- | 1 0 0 1 | --- | --- |
| | JT/SW P-Value | 0.423N | 0.830N | 0.583N | 0.893N | 0.636N | 0.648N |
| | RTE P-Value | 0.435N | 0.149 | 0.500 | 0.037 * | 0.500 | 0.500 |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 1/20 (5.0%) | 1/21 (4.8%) | 0/20 (0.0%) | 2/22 (9.1%) | 2/19 (10.5%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/20 (5.0%) | 1/21 (4.8%) | 0/20 (0.0%) | 2/22 (9.1%) | 2/19 (10.5%) | 0/20 (0.0%) |
| | Time-to-First | 365 (T) | 364 (T) | ---- | 364 (T) | 363 (T) | ---- |
| | CAFE P-Value | 0.534N | 0.744N | 0.500N | 0.537 | 0.480 | 0.476N |
| | Severity Profile | 1 0 0 0 | 0 1 0 0 | --- | 0 2 0 0 | 1 1 0 0 | --- |
| | JT/SW P-Value | 0.491N | 0.500N | 0.231N | 0.618N | 0.712N | 0.317N |
| | RTE P-Value | 0.481 | 0.500 | 0.240N | 0.256 | 0.152 | 0.235N |
| Pituitary Gland * Angiectasis | Simple Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/20 (0.0%) |
| | Time-to-First | ---- | 363 (T) | 365 (T) | ---- | ---- | ---- |
| | CAFE P-Value | 0.154N | 0.268 | 0.500 | | | |
| | Severity Profile | --- | 0 1 1 0 | 0 1 0 0 | --- | --- | --- |
| | JT/SW P-Value | 0.110N | 0.914N | 0.843N | 0.618N | 0.636N | 0.648N |
| | RTE P-Value | 0.145N | 0.015 * | 0.161 | 0.500 | 0.500 | 0.500 |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 3/20 (15.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 3/20 (15.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 2/20 (10.0%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|---------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Time-to-First | 363 (T) | ---- | ---- | ---- | ---- | 362 (T) |
| | CAFE P-Value | 0.291N | 0.099N | 0.115N | 0.099N | 0.115N | 0.453N |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 18/20 (90.0%) | 16/22 (72.7%) | 14/20 (70.0%) | 20/22 (90.9%) | 16/20 (80.0%) | 18/22 (81.8%) |
| | Terminal Incidence | 18/20 (90.0%) | 16/22 (72.7%) | 14/20 (70.0%) | 20/22 (90.9%) | 16/20 (80.0%) | 18/20 (90.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 363 (T) | 362 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.496 | 0.152N | 0.118N | 0.659 | 0.331N | 0.380N |
| | Severity Profile | 10 8 0 0 | 10 4 2 0 | 5 5 4 0 | 10 9 1 0 | 6 7 3 0 | 9 8 1 0 |
| | JT/SW P-Value | 0.273 | 0.861 | 0.626 | 0.450 | 0.440 | 0.546 |
| | RTE P-Value | 0.264 | 0.179N | 0.497 | 0.356 | 0.334 | 0.447N |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 10/20 (50.0%) | 16/22 (72.7%) | 11/20 (55.0%) | 12/22 (54.5%) | 13/20 (65.0%) | 9/22 (40.9%) |
| | Terminal Incidence | 10/20 (50.0%) | 16/22 (72.7%) | 11/20 (55.0%) | 12/22 (54.5%) | 13/20 (65.0%) | 9/20 (45.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.211N | 0.116 | 0.500 | 0.506 | 0.262 | 0.390N |
| | Severity Profile | 10 0 0 0 | 11 4 1 0 | 8 3 0 0 | 8 4 0 0 | 11 2 0 0 | 8 1 0 0 |
| | JT/SW P-Value | 0.204N | 0.982N | 0.859N | 0.896N | 0.927N | 0.492N |
| | RTE P-Value | 0.235N | 0.024 * | 0.221 | 0.194 | 0.126 | 0.367N |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 4/20 (20.0%) | 6/22 (27.3%) | 7/20 (35.0%) | 4/22 (18.2%) | 6/20 (30.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 4/20 (20.0%) | 6/22 (27.3%) | 7/20 (35.0%) | 4/22 (18.2%) | 6/20 (30.0%) | 6/20 (30.0%) |
| | Time-to-First | 363 (T) | 359 (T) | 363 (T) | 363 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.397 | 0.426 | 0.240 | 0.594N | 0.358 | 0.426 |
| Genital System | | | | | | | |
| Ovary * Atrophy | Simple Incidence | 10/20 (50.0%) | 9/22 (40.9%) | 11/20 (55.0%) | 6/22 (27.3%) | 12/20 (60.0%) | 15/22 (68.2%) |
| | Terminal Incidence | 10/20 (50.0%) | 9/22 (40.9%) | 11/20 (55.0%) | 6/22 (27.3%) | 12/20 (60.0%) | 14/20 (70.0%) |
| | Time-to-First | 361 (T) | 363 (T) | 363 (T) | 363 (T) | 363 (T) | 255 |
| | CAFE P-Value | 0.097 | 0.390N | 0.500 | 0.116N | 0.376 | 0.188 |
| | Severity Profile | 2 6 0 2 | 1 4 0 4 | 8 1 0 2 | 1 3 0 2 | 5 4 0 3 | 4 5 0 6 |
| | JT/SW P-Value | 0.094 | 0.588 | 0.709 | 0.856 | 0.449 | 0.131 |
| | RTE P-Value | 0.100 | 0.390N | 0.374N | 0.095N | 0.348 | 0.099 |
| Ovary * Cyst | Simple Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/20 (0.0%) |
| | Time-to-First | ---- | 364 (T) | ---- | ---- | ---- | ---- |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------|--------------------------|----------------|---------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Statistic</i> | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> | |
| | CAFE P-Value | 0.160N | 0.268 | | | | |
| Ovary * Cyst,Corpus Luteum | Simple Incidence | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 5/22 (22.7%) | 1/20 (5.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 5/22 (22.7%) | 1/20 (5.0%) | 0/20 (0.0%) |
| | Time-to-First | 365 (T) | 363 (T) | 364 (T) | 362 (T) | 363 (T) | ---- |
| | CAFE P-Value | 0.201N | 0.659N | 0.698 | 0.247 | 0.500N | 0.221N |
| Ovary * Cyst,Follicle | Simple Incidence | 5/20 (25.0%) | 6/22 (27.3%) | 4/20 (20.0%) | 7/22 (31.8%) | 11/20 (55.0%) | 18/22 (81.8%) |
| | Terminal Incidence | 5/20 (25.0%) | 6/22 (27.3%) | 4/20 (20.0%) | 7/22 (31.8%) | 11/20 (55.0%) | 17/20 (85.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 364 (T) | 363 (T) | 255 |
| | CAFE P-Value | <.001 *** | 0.574 | 0.500N | 0.443 | 0.053 | <.001 *** |
| Ovary * Cyst,Periovarian Tissue | Simple Incidence | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/20 (0.0%) |
| | Time-to-First | ---- | ---- | ---- | 365 (T) | ---- | ---- |
| | CAFE P-Value | 0.424 | | | 0.268 | | |
| Ovary * Depletion,Corpus Luteum | Simple Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 6/20 (30.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.138 | 0.380 | 0.698 | 0.659N | 0.500 | 0.152 |
| Ovary * Diestrus | Simple Incidence | 10/20 (50.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 12/22 (54.5%) | 11/20 (55.0%) | 13/22 (59.1%) |
| | Terminal Incidence | 10/20 (50.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 12/22 (54.5%) | 11/20 (55.0%) | 11/20 (55.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 364 (T) | 362 (T) | 362 (T) | 43 |
| | CAFE P-Value | 0.236 | 0.621 | 0.500N | 0.506 | 0.500 | 0.390 |
| Ovary * Hypertrophy,Interstitial Cell | Simple Incidence | 4/20 (20.0%) | 3/22 (13.6%) | 1/20 (5.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 4/20 (20.0%) | 3/22 (13.6%) | 1/20 (5.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 5/20 (25.0%) |
| | Time-to-First | 363 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.380 | 0.444N | 0.171N | 0.286N | 0.500N | 0.565 |
| | Severity Profile | 0 1 3 0 | 0 2 1 0 | 0 1 0 0 | 0 2 0 0 | 0 3 0 0 | 0 4 1 0 |
| | JT/SW P-Value | 0.400 | 0.739 | 0.919 | 0.951 | 0.865 | 0.601 |
| | RTE P-Value | 0.429 | 0.244N | 0.061N | 0.117N | 0.268N | 0.459 |
| Ovary * Metestrus | Simple Incidence | 7/20 (35.0%) | 5/22 (22.7%) | 4/20 (20.0%) | 4/22 (18.2%) | 5/20 (25.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 7/20 (35.0%) | 5/22 (22.7%) | 4/20 (20.0%) | 4/22 (18.2%) | 5/20 (25.0%) | 2/20 (10.0%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|---------------|--------------|--------------|--------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Time-to-First | 362 (T) | 361 (T) | 363 (T) | 363 (T) | 363 (T) | 365 (T) |
| | CAFE P-Value | 0.055N | 0.296N | 0.240N | 0.188N | 0.366N | 0.047N* |
| Ovary * Proestrus | Simple Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 5/20 (25.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/22 (9.1%) | 5/20 (25.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 1/20 (5.0%) |
| | Time-to-First | 364 (T) | 363 (T) | 363 (T) | 363 (T) | 366 (T) | 364 (T) |
| | CAFE P-Value | 0.382N | 0.537 | 0.091 | 0.203 | 0.756 | 0.732N |
| Uterus * Apoptosis | Simple Incidence | 2/20 (10.0%) | 3/22 (13.6%) | 2/20 (10.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 2/20 (10.0%) | 3/22 (13.6%) | 2/20 (10.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 6/20 (30.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.171 | 0.547 | 0.698 | 0.659N | 0.500N | 0.152 |
| | Severity Profile | 0 0 0 2 | 0 1 0 2 | 0 0 1 1 | 0 0 2 0 | 0 0 0 1 | 0 1 0 5 |
| | JT/SW P-Value | 0.149 | 0.377 | 0.522 | 0.603 | 0.680 | 0.061 |
| | RTE P-Value | 0.161 | 0.382 | 0.479N | 0.425N | 0.312N | 0.055 |
| Uterus * Cyst,Endometrium | Simple Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 2/22 (9.1%) | 3/20 (15.0%) | 0/20 (0.0%) |
| | Time-to-First | ---- | 363 (T) | 365 (T) | 364 (T) | 363 (T) | ---- |
| | CAFE P-Value | 0.314 | 0.524 | 0.244 | 0.268 | 0.115 | |
| Uterus * Diestrus | Simple Incidence | 7/20 (35.0%) | 10/22 (45.5%) | 7/20 (35.0%) | 7/22 (31.8%) | 9/20 (45.0%) | 10/22 (45.5%) |
| | Terminal Incidence | 7/20 (35.0%) | 10/22 (45.5%) | 7/20 (35.0%) | 7/22 (31.8%) | 9/20 (45.0%) | 9/20 (45.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 364 (T) | 363 (T) | 362 (T) | 255 |
| | CAFE P-Value | 0.324 | 0.355 | 0.629 | 0.543N | 0.374 | 0.355 |
| Uterus * Dilatation,Lumen | Simple Incidence | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 4/22 (18.2%) | 1/20 (5.0%) | 0/20 (0.0%) |
| | Time-to-First | 363 (T) | ---- | 363 (T) | 363 (T) | 366 (T) | ---- |
| | CAFE P-Value | 0.515 | 0.476N | 0.756 | 0.203 | 0.756 | 0.476N |
| | Severity Profile | 0 0 0 1 | --- | 0 0 0 1 | 0 0 1 3 | 0 0 1 0 | --- |
| | JT/SW P-Value | 0.485 | 0.853 | 0.583 | 0.064 | 0.264 | 0.473 |
| | RTE P-Value | 0.479 | 0.234N | 0.500 | 0.045 * | 0.485N | 0.234N |
| Uterus * Estrus | Simple Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 6/20 (30.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|---------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | CAFE P-Value | 0.185 | 0.380 | 0.698 | 0.659N | 0.698 | 0.152 |
| Uterus * Hyperplasia,Cystic,Endometrium | Simple Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 7/22 (31.8%) |
| | Terminal Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 7/20 (35.0%) |
| | Time-to-First | 362 (T) | 359 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.148 | 0.380 | 0.698 | 0.659N | 0.500N | 0.088 |
| | Severity Profile | 0 1 0 1 | 0 2 2 0 | 0 2 0 0 | 0 2 0 0 | 0 0 0 1 | 2 4 0 1 |
| | JT/SW P-Value | 0.158 | 0.241 | 0.429 | 0.527 | 0.617 | 0.039 * |
| | RTE P-Value | 0.173 | 0.224 | 0.474N | 0.441N | 0.329N | 0.030 * |
| Uterus * Hyperplasia,Endometrial Glands | Simple Incidence | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 2/20 (10.0%) |
| | Time-to-First | 362 (T) | ---- | 364 (T) | 366 (T) | ---- | 362 (T) |
| | CAFE P-Value | 0.313 | 0.476N | 0.756 | 0.732N | 0.500N | 0.537 |
| | Severity Profile | 0 1 0 0 | --- | 0 1 0 0 | 0 1 0 0 | --- | 0 2 0 0 |
| | JT/SW P-Value | 0.263 | 0.853 | 0.583 | 0.636 | 0.771 | 0.338 |
| | RTE P-Value | 0.290 | 0.207N | 0.500 | 0.470N | 0.212N | 0.252 |
| Uterus * Hyperplasia,Endometrium | Simple Incidence | 6/20 (30.0%) | 9/22 (40.9%) | 5/20 (25.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 9/22 (40.9%) |
| | Terminal Incidence | 6/20 (30.0%) | 9/22 (40.9%) | 5/20 (25.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 9/20 (45.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 364 (T) | 363 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.392 | 0.340 | 0.500N | 0.582 | 0.634 | 0.340 |
| | Severity Profile | 1 4 1 0 | 1 6 2 0 | 2 2 1 0 | 2 4 1 0 | 0 6 0 0 | 0 7 2 0 |
| | JT/SW P-Value | 0.333 | 0.216 | 0.488 | 0.544 | 0.581 | 0.249 |
| | RTE P-Value | 0.338 | 0.211 | 0.340N | 0.486 | 0.499N | 0.190 |
| Uterus * Metaplasia,Squamous | Simple Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 0/20 (0.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 4/20 (20.0%) |
| | Time-to-First | ---- | 364 (T) | 365 (T) | 365 (T) | ---- | 363 (T) |
| | CAFE P-Value | 0.091 | 0.268 | 0.500 | 0.524 | ---- | 0.065 |
| | Severity Profile | --- | 2 0 0 0 | 0 1 0 0 | 1 0 0 0 | --- | 1 3 0 0 |
| | JT/SW P-Value | 0.067 | 0.086 | 0.177 | 0.220 | 0.289 | 0.009 ** |
| | RTE P-Value | 0.067 | 0.134 | 0.190 | 0.278 | 0.500 | 0.005 ** |
| Uterus * Metestrus | Simple Incidence | 8/20 (40.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 8/22 (36.4%) | 7/20 (35.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 8/20 (40.0%) | 7/22 (31.8%) | 6/20 (30.0%) | 8/22 (36.4%) | 7/20 (35.0%) | 3/20 (15.0%) |
| | Time-to-First | 362 (T) | 359 (T) | 363 (T) | 363 (T) | 362 (T) | 43 |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|---------------|----------------|---------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | CAFE P-Value | 0.146N | 0.409N | 0.371N | 0.530N | 0.500N | 0.111N |
| Uterus * Proestrus | Simple Incidence | 2/20 (10.0%) | 1/22 (4.5%) | 5/20 (25.0%) | 5/22 (22.7%) | 2/20 (10.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 2/20 (10.0%) | 1/22 (4.5%) | 5/20 (25.0%) | 5/22 (22.7%) | 2/20 (10.0%) | 2/20 (10.0%) |
| | Time-to-First | 363 (T) | 365 (T) | 363 (T) | 362 (T) | 365 (T) | 362 (T) |
| | CAFE P-Value | 0.464 | 0.463N | 0.204 | 0.247 | 0.698 | 0.659N |
| Vagina * Diestrus | Simple Incidence | 6/20 (30.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 10/22 (45.5%) | 9/20 (45.0%) | 10/22 (45.5%) |
| | Terminal Incidence | 6/20 (30.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 10/22 (45.5%) | 9/20 (45.0%) | 9/20 (45.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 364 (T) | 363 (T) | 362 (T) | 255 |
| | CAFE P-Value | 0.276 | 0.158 | 0.257 | 0.239 | 0.257 | 0.239 |
| Vagina * Estrus | Simple Incidence | 2/20 (10.0%) | 3/22 (13.6%) | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 2/20 (10.0%) | 3/22 (13.6%) | 2/20 (10.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 6/20 (30.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.125 | 0.547 | 0.698 | 0.659N | 0.698 | 0.152 |
| Vagina * Hyperplasia,Epithelium | Simple Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 2/20 (10.0%) | 4/22 (18.2%) | 2/20 (10.0%) | 1/22 (4.5%) | 2/20 (10.0%) | 6/20 (30.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.199 | 0.380 | 0.698 | 0.463N | 0.698 | 0.152 |
| | Severity Profile | 0 0 2 0 | 0 0 4 0 | 0 0 2 0 | 0 0 0 1 | 0 1 1 0 | 0 1 5 0 |
| | JT/SW P-Value | 0.189 | 0.227 | 0.409 | 0.567 | 0.604 | 0.073 |
| | RTE P-Value | 0.201 | 0.219 | 0.500 | 0.320N | 0.477N | 0.064 |
| Vagina * Metestrus | Simple Incidence | 9/20 (45.0%) | 6/22 (27.3%) | 4/20 (20.0%) | 5/22 (22.7%) | 7/20 (35.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 9/20 (45.0%) | 6/22 (27.3%) | 4/20 (20.0%) | 5/22 (22.7%) | 7/20 (35.0%) | 3/20 (15.0%) |
| | Time-to-First | 362 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 43 |
| | CAFE P-Value | 0.105N | 0.191N | 0.088N | 0.115N | 0.374N | 0.061N |
| Vagina * Mucification,Epithelium | Simple Incidence | 8/20 (40.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 11/22 (50.0%) | 8/20 (40.0%) | 10/22 (45.5%) |
| | Terminal Incidence | 8/20 (40.0%) | 11/22 (50.0%) | 9/20 (45.0%) | 11/22 (50.0%) | 8/20 (40.0%) | 9/20 (45.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 364 (T) | 363 (T) | 363 (T) | 255 |
| | CAFE P-Value | 0.515 | 0.367 | 0.500 | 0.367 | 0.626 | 0.483 |
| | Severity Profile | 1 2 1 4 | 0 3 4 4 | 0 3 4 2 | 0 6 2 3 | 0 1 3 4 | 0 2 3 5 |
| | JT/SW P-Value | 0.405 | 0.271 | 0.410 | 0.433 | 0.481 | 0.408 |
| | RTE P-Value | 0.402 | 0.270 | 0.442 | 0.379 | 0.420 | 0.306 |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Vagina * Proestrus | Simple Incidence | 2/20 (10.0%) | 2/22 (9.1%) | 5/20 (25.0%) | 5/22 (22.7%) | 2/20 (10.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 2/20 (10.0%) | 2/22 (9.1%) | 5/20 (25.0%) | 5/22 (22.7%) | 2/20 (10.0%) | 2/20 (10.0%) |
| | Time-to-First | 363 (T) | 363 (T) | 363 (T) | 362 (T) | 365 (T) | 362 (T) |
| | CAFE P-Value | 0.504N | 0.659N | 0.204 | 0.247 | 0.698 | 0.659N |
| Hematopoietic System | | | | | | | |
| Spleen * Hematopoietic Cell Proliferation | Simple Incidence | 2/20 (10.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 3/22 (13.6%) | 3/20 (15.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 2/20 (10.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 3/22 (13.6%) | 3/20 (15.0%) | 1/20 (5.0%) |
| | Time-to-First | 366 (T) | --- | 365 (T) | 364 (T) | 362 (T) | 43 |
| | CAFE P-Value | 0.194 | 0.221N | 0.500N | 0.547 | 0.500 | 0.659N |
| | Severity Profile | 0 2 0 0 | --- | 0 1 0 0 | 0 2 1 0 | 1 1 1 0 | 1 0 1 0 |
| | JT/SW P-Value | 0.168 | 0.933 | 0.846 | 0.398 | 0.381 | 0.510 |
| | RTE P-Value | 0.176 | 0.165N | 0.291N | 0.328 | 0.290 | 0.461N |
| Spleen * Pigmentation | Simple Incidence | 20/20 (100.0%) | 22/22 (100.0%) | 20/20 (100.0%) | 22/22 (100.0%) | 20/20 (100.0%) | 20/22 (90.9%) |
| | Terminal Incidence | 20/20 (100.0%) | 22/22 (100.0%) | 20/20 (100.0%) | 22/22 (100.0%) | 20/20 (100.0%) | 19/20 (95.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 363 (T) | 362 (T) | 362 (T) | 255 |
| | CAFE P-Value | 0.029N* | | | | | 0.268N |
| | Severity Profile | 6 6 5 3 | 2 7 10 3 | 5 8 3 4 | 5 7 9 1 | 0 9 10 1 | 1 6 10 3 |
| | JT/SW P-Value | 0.183 | 0.096 | 0.279 | 0.370 | 0.137 | 0.160 |
| | RTE P-Value | 0.192 | 0.085 | 0.469 | 0.446 | 0.122 | 0.132 |
| Thymus * Atrophy | Simple Incidence | 18/20 (90.0%) | 19/22 (86.4%) | 18/20 (90.0%) | 17/22 (77.3%) | 18/20 (90.0%) | 16/22 (72.7%) |
| | Terminal Incidence | 18/20 (90.0%) | 19/22 (86.4%) | 18/20 (90.0%) | 17/22 (77.3%) | 18/20 (90.0%) | 16/20 (80.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 363 (T) | 362 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.100N | 0.547N | 0.698N | 0.247N | 0.698N | 0.152N |
| | Severity Profile | 0 8 5 5 | 0 8 2 9 | 0 2 4 12 | 0 5 6 6 | 0 5 5 8 | 0 4 4 8 |
| | JT/SW P-Value | 0.464N | 0.640N | 0.938N | 0.571N | 0.792N | 0.690N |
| | RTE P-Value | 0.483N | 0.323 | 0.024 * | 0.457N | 0.189 | 0.462 |
| Integumentary System | | | | | | | |
| Mammary Gland * Dilatation,Duct | Simple Incidence | 4/20 (20.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 4/20 (20.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/20 (5.0%) |
| | Time-to-First | 363 (T) | 364 (T) | 364 (T) | 365 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.046N* | 0.286N | 0.171N | 0.144N | 0.171N | 0.144N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|----------------------|----------------------|----------------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Severity Profile | 2 1 1 0 | 1 1 0 0 | 0 1 0 0 | 1 0 0 0 | 0 1 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.036N* | 0.155N | 0.084N | 0.051N | 0.054N | 0.038N* |
| | RTE P-Value | 0.035N* | 0.073N | 0.053N | 0.026N* | 0.050N | 0.026N* |
| Mammary Gland * Hyperplasia,Lobular | Simple Incidence | 15/20 (75.0%) | 12/22 (54.5%) | 8/20 (40.0%) | 12/22 (54.5%) | 7/20 (35.0%) | 12/22 (54.5%) |
| | Terminal Incidence | 15/20 (75.0%) | 12/22 (54.5%) | 8/20 (40.0%) | 12/22 (54.5%) | 7/20 (35.0%) | 11/20 (55.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 363 (T) | 362 (T) | 363 (T) | 255 |
| | CAFE P-Value | 0.072N | 0.145N | 0.027N* | 0.145N | 0.012N* | 0.145N |
| | Severity Profile | 10 4 1 0 | 8 3 1 0 | 5 1 2 0 | 8 3 1 0 | 4 3 0 0 | 6 4 2 0 |
| | JT/SW P-Value | 0.133N | 0.115N | 0.034N* ¹ | 0.074N | 0.014N* ¹ | 0.079N |
| | RTE P-Value | 0.118N | 0.119N | 0.031N* | 0.119N | 0.015N* | 0.189N |
| Urinary System | | | | | | | |
| Kidney * Casts Protein | Simple Incidence | 3/20 (15.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 3/20 (15.0%) | 1/22 (4.5%) | 1/20 (5.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/20 (5.0%) |
| | Time-to-First | 362 (T) | 365 (T) | 365 (T) | ---- | 363 (T) | 365 (T) |
| | CAFE P-Value | 0.123N | 0.267N | 0.302N | 0.099N | 0.302N | 0.267N |
| | Severity Profile | 3 0 0 0 | 1 0 0 0 | 1 0 0 0 | --- | 1 0 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.099N | 0.127N | 0.142N | 0.025N* ¹ | 0.055N | 0.060N |
| | RTE P-Value | 0.094N | 0.061N | 0.094N | 0.037N* | 0.094N | 0.061N |
| Kidney * Cyst,Cortex | Simple Incidence | 3/20 (15.0%) | 2/22 (9.1%) | 6/20 (30.0%) | 4/22 (18.2%) | 7/20 (35.0%) | 3/22 (13.6%) |
| | Terminal Incidence | 3/20 (15.0%) | 2/22 (9.1%) | 6/20 (30.0%) | 4/22 (18.2%) | 7/20 (35.0%) | 3/20 (15.0%) |
| | Time-to-First | 364 (T) | 359 (T) | 364 (T) | 363 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.242 | 0.453N | 0.225 | 0.556 | 0.137 | 0.620N |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 4/20 (20.0%) | 3/22 (13.6%) | 4/20 (20.0%) | 4/22 (18.2%) | 6/20 (30.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 4/20 (20.0%) | 3/22 (13.6%) | 4/20 (20.0%) | 4/22 (18.2%) | 6/20 (30.0%) | 5/20 (25.0%) |
| | Time-to-First | 362 (T) | 363 (T) | 364 (T) | 364 (T) | 362 (T) | 363 (T) |
| | CAFE P-Value | 0.226 | 0.444N | 0.653 | 0.594N | 0.358 | 0.565 |
| Kidney * Mineralization | Simple Incidence | 13/20 (65.0%) | 11/22 (50.0%) | 11/20 (55.0%) | 14/22 (63.6%) | 13/20 (65.0%) | 11/22 (50.0%) |
| | Terminal Incidence | 13/20 (65.0%) | 11/22 (50.0%) | 11/20 (55.0%) | 14/22 (63.6%) | 13/20 (65.0%) | 11/20 (55.0%) |
| | Time-to-First | 361 (T) | 359 (T) | 363 (T) | 362 (T) | 362 (T) | 363 (T) |
| | CAFE P-Value | 0.428N | 0.252N | 0.374N | 0.591N | 0.629N | 0.252N |
| | Severity Profile | 8 4 0 1 | 9 2 0 0 | 6 4 0 1 | 8 6 0 0 | 6 6 1 0 | 8 3 0 0 |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 7. Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm</i> | | | | | | | | |
|---|--------------------|--------------------------|---------------|---------------|---------------|---------------|---------------|--|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> | |
| | JT/SW P-Value | 0.466N | 0.093N | 0.225N | 0.346N | 0.465N | 0.169N | |
| | RTE P-Value | 0.470N | 0.100N | 0.326N | 0.477N | 0.376 | 0.128N | |
| Kidney * Nephropathy | Simple Incidence | 10/20 (50.0%) | 10/22 (45.5%) | 10/20 (50.0%) | 11/22 (50.0%) | 12/20 (60.0%) | 13/22 (59.1%) | |
| | Terminal Incidence | 10/20 (50.0%) | 10/22 (45.5%) | 10/20 (50.0%) | 11/22 (50.0%) | 12/20 (60.0%) | 12/20 (60.0%) | |
| | Time-to-First | 361 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 43 | |
| | CAFE P-Value | 0.177 | 0.506N | 0.624N | 0.621 | 0.376 | 0.390 | |
| | Severity Profile | 7 2 1 0 | 7 2 1 0 | 9 1 0 0 | 7 3 1 0 | 7 5 0 0 | 10 1 1 1 | |
| | JT/SW P-Value | 0.157 | 0.610 | 0.704 | 0.580 | 0.302 | 0.364 | |
| | RTE P-Value | 0.169 | 0.392N | 0.372N | 0.465 | 0.230 | 0.319 | |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.

| <i>Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|---------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Alimentary System | | | | | | | |
| Liver * Basophilic Focus | Simple Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 0/20 (0.0%) | 0/19 (0.0%) | 0/20 (0.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 0/19 (0.0%) | 0/19 (0.0%) | 0/20 (0.0%) | 1/22 (4.5%) |
| | Time-to-First | 364 (T) | 363 (T) | ---- | ---- | ---- | 365 (T) |
| | CAFE P-Value | 0.226N | 0.500 | 0.500N | 0.513N | 0.500N | 0.732N |
| Liver * Degeneration,Cystic | Simple Incidence | 4/20 (20.0%) | 4/20 (20.0%) | 3/20 (15.0%) | 1/19 (5.3%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 4/20 (20.0%) | 4/20 (20.0%) | 3/19 (15.8%) | 1/19 (5.3%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Time-to-First | 364 (T) | 364 (T) | 364 (T) | 365 (T) | ---- | ---- |
| | CAFE P-Value | 0.001N** | 0.653 | 0.500N | 0.187N | 0.053N | 0.043N* |
| | Severity Profile | 3 1 0 0 | 4 0 0 0 | 3 0 0 0 | 1 0 0 0 | --- | --- |
| | JT/SW P-Value | 0.001N** | 0.469N | 0.379N | 0.117N | 0.030N* | 0.017N* |
| RTE P-Value | 0.001N** | 0.479N | 0.279N | 0.039N* | 0.010N* | 0.013N* | |
| Liver * Fatty Change | Simple Incidence | 0/20 (0.0%) | 1/20 (5.0%) | 1/20 (5.0%) | 0/19 (0.0%) | 2/20 (10.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 0/20 (0.0%) | 1/20 (5.0%) | 1/19 (5.3%) | 0/19 (0.0%) | 2/20 (10.0%) | 1/22 (4.5%) |
| | Time-to-First | ---- | 363 (T) | 365 (T) | ---- | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.235 | 0.500 | 0.500 | 0.244 | 0.524 | 0.524 |
| | Severity Profile | --- | 0 1 0 0 | 0 0 1 0 | --- | 0 0 2 0 | 0 0 1 0 |
| | JT/SW P-Value | 0.186 | 0.159 | 0.224 | 0.322 | 0.067 | 0.163 |
| RTE P-Value | 0.179 | 0.224 | 0.215 | 0.500 | 0.082 | 0.231 | |
| Liver * Hepatodiaphragmatic Nodule | Simple Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 3/20 (15.0%) | 3/19 (15.8%) | 2/20 (10.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 2/19 (10.5%) | 3/19 (15.8%) | 2/20 (10.0%) | 1/22 (4.5%) |
| | Time-to-First | 363 (T) | 363 (T) | 131 | 364 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.503N | 0.500 | 0.302 | 0.283 | 0.500 | 0.732N |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 8/20 (40.0%) | 9/20 (45.0%) | 5/20 (25.0%) | 5/19 (26.3%) | 5/20 (25.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 8/20 (40.0%) | 9/20 (45.0%) | 5/19 (26.3%) | 5/19 (26.3%) | 5/20 (25.0%) | 5/22 (22.7%) |
| | Time-to-First | 361 (T) | 361 (T) | 364 (T) | 363 (T) | 365 (T) | 363 (T) |
| | CAFE P-Value | 0.051N | 0.500 | 0.250N | 0.286N | 0.250N | 0.191N |
| | Severity Profile | 7 1 0 0 | 8 1 0 0 | 4 1 0 0 | 3 2 0 0 | 4 1 0 0 | 5 0 0 0 |
| | JT/SW P-Value | 0.049N* | 0.616N | 0.215N | 0.268N | 0.231N | 0.142N |
| RTE P-Value | 0.049N* | 0.375 | 0.168N | 0.227N | 0.171N | 0.110N | |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 11/20 (55.0%) | 13/20 (65.0%) | 9/20 (45.0%) | 13/19 (68.4%) | 11/20 (55.0%) | 15/22 (68.2%) |

| <i>Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|----------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 11/20 (55.0%) | 13/20 (65.0%) | 9/19 (47.4%) | 13/19 (68.4%) | 11/20 (55.0%) | 15/22 (68.2%) |
| | Time-to-First | 364 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.268 | 0.374 | 0.376N | 0.298 | 0.624N | 0.288 |
| | Severity Profile | 11 0 0 0 | 13 0 0 0 | 9 0 0 0 | 13 0 0 0 | 11 0 0 0 | 15 0 0 0 |
| | JT/SW P-Value | 0.249 | 0.262 | 0.583 | 0.255 | 0.445 | 0.262 |
| | RTE P-Value | 0.259 | 0.262 | 0.262N | 0.192 | 0.500 | 0.201 |
| Liver * Tension Lipidosis | Simple Incidence | 1/20 (5.0%) | 0/20 (0.0%) | 3/20 (15.0%) | 2/19 (10.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/20 (5.0%) | 0/20 (0.0%) | 3/19 (15.8%) | 2/19 (10.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Time-to-First | 365 (T) | --- | 363 (T) | 364 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.300 | 0.500N | 0.302 | 0.480 | 0.756 | 0.537 |
| | Severity Profile | 0 1 0 0 | --- | 0 1 1 1 | 0 0 2 0 | 0 0 1 0 | 0 0 2 0 |
| | JT/SW P-Value | 0.251 | 0.841 | 0.115 | 0.215 | 0.331 | 0.352 |
| | RTE P-Value | 0.250 | 0.287N | 0.087 | 0.186 | 0.484 | 0.294 |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 6/20 (30.0%) | 5/20 (25.0%) | 10/20 (50.0%) | 5/19 (26.3%) | 4/20 (20.0%) | 8/22 (36.4%) |
| | Terminal Incidence | 6/20 (30.0%) | 5/20 (25.0%) | 10/19 (52.6%) | 5/19 (26.3%) | 4/20 (20.0%) | 8/22 (36.4%) |
| | Time-to-First | 360 (T) | 364 (T) | 363 (T) | 364 (T) | 365 (T) | 363 (T) |
| | CAFE P-Value | 0.504N | 0.500N | 0.167 | 0.540N | 0.358N | 0.457 |
| | Severity Profile | 4 2 0 0 | 3 2 0 0 | 5 5 0 0 | 3 2 0 0 | 3 1 0 0 | 6 2 0 0 |
| | JT/SW P-Value | 0.444N | 0.378N | 0.803N | 0.531N | 0.323N | 0.572N |
| | RTE P-Value | 0.424N | 0.384N | 0.064 | 0.419N | 0.243N | 0.357 |
| Pancreas * Degeneration,Acinus | Simple Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 12/20 (60.0%) | 17/19 (89.5%) | 18/20 (90.0%) | 20/22 (90.9%) |
| | Terminal Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 12/19 (63.2%) | 17/19 (89.5%) | 18/20 (90.0%) | 20/22 (90.9%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.404 | 0.500 | 0.032N* | 0.678N | 0.698N | 0.659 |
| | Severity Profile | 2 9 5 2 | 3 9 4 3 | 3 5 3 1 | 5 6 4 2 | 3 8 7 0 | 8 8 3 1 |
| | JT/SW P-Value | 0.109N | 0.563N | 0.019N* ¹ | 0.102N | 0.191N | 0.089N |
| | RTE P-Value | 0.102N | 0.428 | 0.009N** | 0.255N | 0.371N | 0.065N |
| Pancreas * Pigmentation | Simple Incidence | 11/20 (55.0%) | 8/20 (40.0%) | 9/20 (45.0%) | 8/19 (42.1%) | 8/20 (40.0%) | 10/22 (45.5%) |
| | Terminal Incidence | 11/20 (55.0%) | 8/20 (40.0%) | 9/19 (47.4%) | 8/19 (42.1%) | 8/20 (40.0%) | 10/22 (45.5%) |
| | Time-to-First | 360 (T) | 363 (T) | 363 (T) | 363 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.318N | 0.264N | 0.376N | 0.314N | 0.264N | 0.379N |
| | Severity Profile | 5 6 0 0 | 8 0 0 0 | 6 3 0 0 | 6 2 0 0 | 8 0 0 0 | 7 3 0 0 |
| | JT/SW P-Value | 0.203N | 0.053N | 0.120N | 0.136N | 0.064N | 0.125N |

| Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm | | | | | | | |
|---|--------------------|--------------------------|----------------|----------------|----------------|----------------|----------------|
| System and Nonneoplasm | | Treatment (ug/kg) | | | | | |
| Lesion | Statistic | Control | 2.5 | 25 | 250 | 2500 | 25000 |
| | RTE P-Value | 0.196N | 0.058N | 0.175N | 0.122N | 0.057N | 0.163N |
| Cardiovascular System | | | | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 17/20 (85.0%) | 20/20 (100.0%) | 19/20 (95.0%) | 13/19 (68.4%) | 18/20 (90.0%) | 19/22 (86.4%) |
| | Terminal Incidence | 17/20 (85.0%) | 20/20 (100.0%) | 19/19 (100.0%) | 13/19 (68.4%) | 18/20 (90.0%) | 19/22 (86.4%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.242N | 0.115 | 0.302 | 0.199N | 0.500 | 0.620 |
| | Severity Profile | 12 3 2 0 | 10 7 2 1 | 7 7 3 2 | 10 3 0 0 | 14 3 1 0 | 9 8 2 0 |
| | JT/SW P-Value | 0.258N | 0.971N | 0.994N | 0.148N | 0.329N | 0.609N |
| | RTE P-Value | 0.201N | 0.027 * | 0.006 ** | 0.098N | 0.441N | 0.150 |
| Endocrine System | | | | | | | |
| Adrenal Cortex * Vacuolization Cytoplasmic | Simple Incidence | 2/20 (10.0%) | 3/20 (15.0%) | 3/20 (15.0%) | 3/19 (15.8%) | 3/20 (15.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 2/20 (10.0%) | 3/20 (15.0%) | 3/19 (15.8%) | 3/19 (15.8%) | 3/20 (15.0%) | 2/22 (9.1%) |
| | Time-to-First | 365 (T) | 364 (T) | 364 (T) | 365 (T) | 363 (T) | 365 (T) |
| | CAFE P-Value | 0.494N | 0.500 | 0.500 | 0.475 | 0.500 | 0.659N |
| | Severity Profile | 0 2 0 0 | 0 3 0 0 | 0 3 0 0 | 2 1 0 0 | 1 2 0 0 | 0 1 1 0 |
| | JT/SW P-Value | 0.455N | 0.682N | 0.764N | 0.777N | 0.795N | 0.630N |
| | RTE P-Value | 0.472N | 0.322 | 0.322 | 0.341 | 0.343 | 0.484N |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 4/20 (20.0%) | 9/20 (45.0%) | 3/19 (15.8%) | 7/19 (36.8%) | 4/19 (21.1%) | 8/22 (36.4%) |
| | Terminal Incidence | 4/20 (20.0%) | 9/20 (45.0%) | 3/18 (16.7%) | 7/19 (36.8%) | 4/19 (21.1%) | 8/22 (36.4%) |
| | Time-to-First | 364 (T) | 361 (T) | 363 (T) | 363 (T) | 364 (T) | 364 (T) |
| | CAFE P-Value | 0.367 | 0.088 | 0.531N | 0.209 | 0.622 | 0.204 |
| | Severity Profile | 1 2 1 0 | 7 1 1 0 | 1 2 0 0 | 5 2 0 0 | 4 0 0 0 | 1 6 1 0 |
| | JT/SW P-Value | 0.297 | 0.090 | 0.345 | 0.243 | 0.424 | 0.129 |
| | RTE P-Value | 0.324 | 0.084 | 0.355N | 0.199 | 0.399N | 0.098 |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 0/20 (0.0%) | 1/19 (5.3%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/20 (5.0%) | 2/20 (10.0%) | 0/19 (0.0%) | 1/19 (5.3%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Time-to-First | 364 (T) | 364 (T) | ---- | 364 (T) | ---- | 365 (T) |
| | CAFE P-Value | 0.526N | 0.500 | 0.500N | 0.744 | 0.500N | 0.537 |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 8/20 (40.0%) | 9/20 (45.0%) | 3/20 (15.0%) | 4/19 (21.1%) | 4/20 (20.0%) | 7/22 (31.8%) |
| | Terminal Incidence | 8/20 (40.0%) | 9/20 (45.0%) | 3/19 (15.8%) | 4/19 (21.1%) | 4/20 (20.0%) | 7/22 (31.8%) |
| | Time-to-First | 361 (T) | 361 (T) | 363 (T) | 364 (T) | 364 (T) | 364 (T) |

| <i>Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------|--------------------------|---------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | CAFE P-Value | 0.118N | 0.500 | 0.078N | 0.175N | 0.150N | 0.409N |
| | Severity Profile | 8 0 0 0 | 7 1 0 1 | 0 3 0 0 | 4 0 0 0 | 4 0 0 0 | 6 1 0 0 |
| | JT/SW P-Value | 0.115N | 0.712N | 0.139N | 0.139N | 0.122N | 0.184N |
| | RTE P-Value | 0.093N | 0.295 | 0.089N | 0.105N | 0.093N | 0.323N |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 13/20 (65.0%) | 9/20 (45.0%) | 10/20 (50.0%) | 11/19 (57.9%) | 10/20 (50.0%) | 12/22 (54.5%) |
| | Terminal Incidence | 13/20 (65.0%) | 9/20 (45.0%) | 10/19 (52.6%) | 11/19 (57.9%) | 10/20 (50.0%) | 12/22 (54.5%) |
| | Time-to-First | 360 (T) | 363 (T) | 364 (T) | 363 (T) | 363 (T) | 363 (T) |
| | CAFE P-Value | 0.400N | 0.170N | 0.262N | 0.450N | 0.262N | 0.355N |
| | Severity Profile | 5 7 1 0 | 1 4 4 0 | 6 2 2 0 | 3 7 1 0 | 7 2 1 0 | 5 5 2 0 |
| | JT/SW P-Value | 0.257N | 0.365N | 0.200N | 0.354N | 0.139N | 0.247N |
| | RTE P-Value | 0.242N | 0.303N | 0.159N | 0.414N | 0.111N | 0.288N |
| Thyroid Gland * Hyperplasia,Follicular Cell | Simple Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 4/20 (20.0%) | 1/19 (5.3%) | 0/20 (0.0%) | 3/22 (13.6%) |
| | Terminal Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 4/19 (21.1%) | 1/19 (5.3%) | 0/20 (0.0%) | 3/22 (13.6%) |
| | Time-to-First | 364 (T) | 365 (T) | 364 (T) | 364 (T) | ---- | 362 (T) |
| | CAFE P-Value | 0.417 | 0.756 | 0.171 | 0.744 | 0.500N | 0.341 |
| | Severity Profile | 0 0 1 0 | 0 0 1 0 | 0 1 3 0 | 0 0 1 0 | --- | 0 0 3 0 |
| | JT/SW P-Value | 0.367 | 0.500 | 0.072 | 0.257 | 0.445 | 0.208 |
| | RTE P-Value | 0.391 | 0.500 | 0.061 | 0.488 | 0.281N | 0.153 |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 6/20 (30.0%) | 3/20 (15.0%) | 9/20 (45.0%) | 5/19 (26.3%) | 4/20 (20.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 6/20 (30.0%) | 3/20 (15.0%) | 9/19 (47.4%) | 5/19 (26.3%) | 4/20 (20.0%) | 5/22 (22.7%) |
| | Time-to-First | 360 (T) | 363 (T) | 363 (T) | 364 (T) | 362 (T) | 364 (T) |
| | CAFE P-Value | 0.331N | 0.225N | 0.257 | 0.540N | 0.358N | 0.426N |
| Genital System | | | | | | | |
| Epididymis * Exfoliated Germ Cell | Simple Incidence | 0/20 (0.0%) | 3/20 (15.0%) | 1/20 (5.0%) | 2/19 (10.5%) | 1/20 (5.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 0/20 (0.0%) | 3/20 (15.0%) | 1/19 (5.3%) | 2/19 (10.5%) | 1/20 (5.0%) | 1/22 (4.5%) |
| | Time-to-First | ---- | 361 (T) | 364 (T) | 363 (T) | 365 (T) | 365 (T) |
| | CAFE P-Value | 0.516N | 0.115 | 0.500 | 0.231 | 0.500 | 0.524 |
| | Severity Profile | --- | 1 2 0 0 | 0 1 0 0 | 2 0 0 0 | 0 1 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.462N | 0.962N | 0.821N | 0.908N | 0.864N | 0.857N |
| | RTE P-Value | 0.474N | 0.034 * | 0.258 | 0.150 | 0.258 | 0.285 |
| Epididymis * Hyospermia | Simple Incidence | 1/20 (5.0%) | 4/20 (20.0%) | 2/20 (10.0%) | 1/19 (5.3%) | 3/20 (15.0%) | 1/22 (4.5%) |

| Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm | | | | | | | |
|---|--------------------|--------------------------|----------------|----------------|----------------|----------------|----------------|
| System and Nonneoplasm | Statistic | Treatment (ug/kg) | | | | | |
| Lesion | Control | 2.5 | 25 | 250 | 2500 | 25000 | |
| | Terminal Incidence | 1/20 (5.0%) | 4/20 (20.0%) | 2/19 (10.5%) | 1/19 (5.3%) | 3/20 (15.0%) | 1/22 (4.5%) |
| | Time-to-First | 360 (T) | 361 (T) | 364 (T) | 365 (T) | 362 (T) | 364 (T) |
| | CAFE P-Value | 0.368N | 0.171 | 0.500 | 0.744 | 0.302 | 0.732N |
| | Severity Profile | 0 0 0 1 | 0 0 0 4 | 0 0 0 2 | 0 0 0 1 | 0 0 0 3 | 0 0 0 1 |
| | JT/SW P-Value | 0.332N | 0.922N | 0.774N | 0.629N | 0.832N | 0.626N |
| | RTE P-Value | 0.346N | 0.076 | 0.300 | 0.489 | 0.157 | 0.481N |
| Epididymis * Infiltration Cellular,Lymphocyte | Simple Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 4/20 (20.0%) | 1/19 (5.3%) | 2/20 (10.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 4/19 (21.1%) | 1/19 (5.3%) | 2/20 (10.0%) | 2/22 (9.1%) |
| | Time-to-First | 365 (T) | 364 (T) | 364 (T) | 364 (T) | 365 (T) | 363 (T) |
| | CAFE P-Value | 0.388 | 0.756 | 0.171 | 0.744 | 0.500 | 0.537 |
| | Severity Profile | 1 0 0 0 | 1 0 0 0 | 4 0 0 0 | 1 0 0 0 | 2 0 0 0 | 2 0 0 0 |
| | JT/SW P-Value | 0.350 | 0.500 | 0.068 | 0.252 | 0.300 | 0.334 |
| | RTE P-Value | 0.349 | 0.500 | 0.079 | 0.489 | 0.293 | 0.324 |
| Prostate, Dorsal/Lateral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 9/20 (45.0%) | 5/20 (25.0%) | 4/20 (20.0%) | 8/18 (44.4%) | 8/20 (40.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 9/20 (45.0%) | 5/20 (25.0%) | 3/19 (15.8%) | 8/18 (44.4%) | 8/20 (40.0%) | 6/22 (27.3%) |
| | Time-to-First | 363 (T) | 361 (T) | 131 | 363 (T) | 364 (T) | 364 (T) |
| | CAFE P-Value | 0.420N | 0.160N | 0.088N | 0.615N | 0.500N | 0.191N |
| | Severity Profile | 9 0 0 0 | 4 1 0 0 | 3 1 0 0 | 8 0 0 0 | 5 3 0 0 | 6 0 0 0 |
| | JT/SW P-Value | 0.428N | 0.124N | 0.072N | 0.231N | 0.338N | 0.167N |
| | RTE P-Value | 0.455N | 0.128N | 0.076N | 0.486N | 0.495 | 0.124N |
| Prostate, Dorsal/Lateral Lobe * Inflammation,Suppurative | Simple Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 16/20 (80.0%) | 16/18 (88.9%) | 19/20 (95.0%) | 18/22 (81.8%) |
| | Terminal Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 16/19 (84.2%) | 16/18 (88.9%) | 19/20 (95.0%) | 18/22 (81.8%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.312N | 0.500 | 0.331N | 0.656N | 0.500 | 0.380N |
| | Severity Profile | 5 13 0 0 | 12 7 0 0 | 6 10 0 0 | 7 9 0 0 | 9 10 0 0 | 5 12 1 0 |
| | JT/SW P-Value | 0.457 | 0.937 | 0.923 | 0.892 | 0.872 | 0.812 |
| | RTE P-Value | 0.460 | 0.083N | 0.146N | 0.215N | 0.262N | 0.340N |
| Prostate, Ventral Lobe * Hyperplasia,Epithelium | Simple Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 0/20 (0.0%) | 2/18 (11.1%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/20 (5.0%) | 1/20 (5.0%) | 0/19 (0.0%) | 2/18 (11.1%) | 0/20 (0.0%) | 0/22 (0.0%) |
| | Time-to-First | 361 (T) | 364 (T) | ---- | 364 (T) | ---- | ---- |
| | CAFE P-Value | 0.229N | 0.756 | 0.500N | 0.459 | 0.500N | 0.476N |
| | Severity Profile | 0 1 0 0 | 0 1 0 0 | --- | 2 0 0 0 | --- | --- |
| | JT/SW P-Value | 0.171N | 0.500N | 0.229N | 0.618N | 0.277N | 0.244N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm | | | | | | | |
|---|--------------------|--------------------------|---------------|---------------|---------------|---------------|---------------|
| System and Nonneoplasm | | Treatment (ug/kg) | | | | | |
| Lesion | Statistic | Control | 2.5 | 25 | 250 | 2500 | 25000 |
| | RTE P-Value | 0.194N | 0.500 | 0.104N | 0.101 | 0.105N | 0.140N |
| Prostate, Ventral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 9/20 (45.0%) | 8/20 (40.0%) | 9/20 (45.0%) | 9/18 (50.0%) | 8/20 (40.0%) | 9/22 (40.9%) |
| | Terminal Incidence | 9/20 (45.0%) | 8/20 (40.0%) | 8/19 (42.1%) | 9/18 (50.0%) | 8/20 (40.0%) | 9/22 (40.9%) |
| | Time-to-First | 360 (T) | 361 (T) | 131 | 363 (T) | 362 (T) | 363 (T) |
| | CAFE P-Value | 0.448N | 0.500N | 0.624 | 0.507 | 0.500N | 0.517N |
| | Severity Profile | 8 1 0 0 | 7 1 0 0 | 8 1 0 0 | 8 1 0 0 | 7 1 0 0 | 9 0 0 0 |
| | JT/SW P-Value | 0.384N | 0.384N | 0.519N | 0.615N | 0.501N | 0.467N |
| | RTE P-Value | 0.395N | 0.384N | 0.500 | 0.382 | 0.384N | 0.351N |
| Prostate, Ventral Lobe * Inflammation,Suppurative | Simple Incidence | 3/20 (15.0%) | 2/20 (10.0%) | 2/20 (10.0%) | 6/18 (33.3%) | 4/20 (20.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 3/20 (15.0%) | 2/20 (10.0%) | 2/19 (10.5%) | 6/18 (33.3%) | 4/20 (20.0%) | 2/22 (9.1%) |
| | Time-to-First | 364 (T) | 361 (T) | 364 (T) | 364 (T) | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.423 | 0.500N | 0.500N | 0.173 | 0.500 | 0.453N |
| | Severity Profile | 2 1 0 0 | 2 0 0 0 | 2 0 0 0 | 6 0 0 0 | 4 0 0 0 | 2 0 0 0 |
| | JT/SW P-Value | 0.425 | 0.698 | 0.789 | 0.098 | 0.259 | 0.478 |
| | RTE P-Value | 0.385 | 0.310N | 0.310N | 0.082 | 0.359 | 0.278N |
| Testes * Degeneration,Seminiferous Tubule | Simple Incidence | 6/20 (30.0%) | 7/20 (35.0%) | 9/20 (45.0%) | 4/19 (21.1%) | 9/20 (45.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 6/20 (30.0%) | 7/20 (35.0%) | 9/19 (47.4%) | 4/19 (21.1%) | 9/20 (45.0%) | 6/22 (27.3%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 363 (T) |
| | CAFE P-Value | 0.477N | 0.500 | 0.257 | 0.394N | 0.257 | 0.557N |
| | Severity Profile | 5 0 0 1 | 3 0 0 4 | 6 1 0 2 | 3 0 0 1 | 6 0 0 3 | 4 1 0 1 |
| | JT/SW P-Value | 0.437N | 0.728N | 0.872N | 0.390N | 0.764N | 0.603N |
| | RTE P-Value | 0.454N | 0.263 | 0.149 | 0.308N | 0.132 | 0.461N |
| Hematopoietic System | | | | | | | |
| Bone Marrow * Hyperplasia,Myeloid Cell | Simple Incidence | 0/20 (0.0%) | 0/20 (0.0%) | 2/20 (10.0%) | 0/19 (0.0%) | 1/20 (5.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/20 (0.0%) | 0/20 (0.0%) | 2/19 (10.5%) | 0/19 (0.0%) | 1/20 (5.0%) | 0/22 (0.0%) |
| | Time-to-First | ---- | ---- | 363 (T) | ---- | 365 (T) | ---- |
| | CAFE P-Value | 0.514 | ---- | 0.244 | ---- | 0.500 | ---- |
| | Severity Profile | --- | --- | 0 0 1 1 | --- | 0 0 1 0 | --- |
| | JT/SW P-Value | 0.453 | 0.500 | 0.047 * 1 | 0.198 | 0.232 | 0.300 |
| | RTE P-Value | 0.433 | 0.500 | 0.020 * | 0.500 | 0.165 | 0.500 |
| Spleen * Hematopoietic Cell Proliferation | Simple Incidence | 0/20 (0.0%) | 1/20 (5.0%) | 0/20 (0.0%) | 0/19 (0.0%) | 1/20 (5.0%) | 2/22 (9.1%) |

| <i>Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 0/20 (0.0%) | 1/20 (5.0%) | 0/19 (0.0%) | 0/19 (0.0%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Time-to-First | ---- | 363 (T) | ---- | ---- | 365 (T) | 364 (T) |
| | CAFE P-Value | 0.105 | 0.500 | | | 0.500 | 0.268 |
| | Severity Profile | --- | 0 0 1 0 | --- | --- | 0 0 1 0 | 1 0 1 0 |
| | JT/SW P-Value | 0.079 | 0.159 | 0.323 | 0.406 | 0.173 | 0.067 |
| | RTE P-Value | 0.097 | 0.194 | 0.500 | 0.500 | 0.195 | 0.090 |
| Spleen * Pigmentation | | | | | | | |
| | Simple Incidence | 12/20 (60.0%) | 14/20 (70.0%) | 13/20 (65.0%) | 18/19 (94.7%) | 15/20 (75.0%) | 18/22 (81.8%) |
| | Terminal Incidence | 12/20 (60.0%) | 14/20 (70.0%) | 13/19 (68.4%) | 18/19 (94.7%) | 15/20 (75.0%) | 18/22 (81.8%) |
| | Time-to-First | 363 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 363 (T) |
| | CAFE P-Value | 0.035 * | 0.371 | 0.500 | 0.012 * | 0.250 | 0.111 |
| | Severity Profile | 4 6 2 0 | 5 9 0 0 | 7 5 1 0 | 11 7 0 0 | 5 10 0 0 | 6 11 0 1 |
| | JT/SW P-Value | 0.068 | 0.398 | 0.577 | 0.241 | 0.298 | 0.148 |
| | RTE P-Value | 0.084 | 0.386 | 0.358N | 0.225 | 0.256 | 0.115 |
| Thymus * Atrophy | | | | | | | |
| | Simple Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 17/20 (85.0%) | 18/19 (94.7%) | 18/20 (90.0%) | 21/22 (95.5%) |
| | Terminal Incidence | 18/20 (90.0%) | 19/20 (95.0%) | 17/19 (89.5%) | 18/19 (94.7%) | 18/20 (90.0%) | 21/22 (95.5%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.363 | 0.500 | 0.500N | 0.520 | 0.698N | 0.463 |
| | Severity Profile | 0 0 6 12 | 0 2 5 12 | 1 3 3 10 | 0 4 3 11 | 0 0 3 15 | 0 5 2 14 |
| | JT/SW P-Value | 0.333 | 0.525 | 0.792 | 0.761 | 0.299 | 0.497 |
| | RTE P-Value | 0.324 | 0.490N | 0.146N | 0.368N | 0.231 | 0.473N |
| Integumentary System | | | | | | | |
| Mammary Gland * Hyperplasia,Lobular | | | | | | | |
| | Simple Incidence | 0/19 (0.0%) | 1/20 (5.0%) | 2/20 (10.0%) | 2/19 (10.5%) | 0/17 (0.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 0/19 (0.0%) | 1/20 (5.0%) | 1/19 (5.3%) | 2/19 (10.5%) | 0/17 (0.0%) | 1/22 (4.5%) |
| | Time-to-First | ---- | 363 (T) | 131 | 365 (T) | ---- | 365 (T) |
| | CAFE P-Value | 0.464 | 0.513 | 0.256 | 0.243 | | 0.537 |
| | Severity Profile | --- | 1 0 0 0 | 1 1 0 0 | 1 1 0 0 | --- | 1 0 0 0 |
| | JT/SW P-Value | 0.406 | 0.165 | 0.092 | 0.117 | 0.223 | 0.239 |
| | RTE P-Value | 0.423 | 0.246 | 0.073 | 0.078 | 0.500 | 0.261 |
| Urinary System | | | | | | | |
| Kidney * Cyst,Cortex | | | | | | | |
| | Simple Incidence | 2/20 (10.0%) | 4/20 (20.0%) | 6/20 (30.0%) | 6/19 (31.6%) | 6/20 (30.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 2/20 (10.0%) | 4/20 (20.0%) | 6/19 (31.6%) | 6/19 (31.6%) | 6/20 (30.0%) | 4/22 (18.2%) |
| | Time-to-First | 364 (T) | 364 (T) | 363 (T) | 364 (T) | 362 (T) | 362 (T) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 8. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Stop Dose Arm</i> | | | | | | | |
|---|--------------------|--------------------------|----------------|----------------|---------------|----------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | CAFE P-Value | 0.212 | 0.331 | 0.118 | 0.101 | 0.118 | 0.380 |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 5/20 (25.0%) | 4/20 (20.0%) | 8/20 (40.0%) | 6/19 (31.6%) | 6/20 (30.0%) | 8/22 (36.4%) |
| | Terminal Incidence | 5/20 (25.0%) | 4/20 (20.0%) | 8/19 (42.1%) | 6/19 (31.6%) | 6/20 (30.0%) | 8/22 (36.4%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 364 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.194 | 0.500N | 0.250 | 0.460 | 0.500 | 0.323 |
| Kidney * Nephropathy | Simple Incidence | 19/20 (95.0%) | 20/20 (100.0%) | 19/20 (95.0%) | 17/19 (89.5%) | 20/20 (100.0%) | 21/22 (95.5%) |
| | Terminal Incidence | 19/20 (95.0%) | 20/20 (100.0%) | 19/19 (100.0%) | 17/19 (89.5%) | 20/20 (100.0%) | 21/22 (95.5%) |
| | Time-to-First | 360 (T) | 361 (T) | 363 (T) | 363 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.519N | 0.500 | 0.756N | 0.480N | 0.500 | 0.732 |
| | Severity Profile | 5 11 3 0 | 6 11 3 0 | 7 5 4 3 | 10 4 2 1 | 6 10 3 1 | 10 3 4 4 |
| | JT/SW P-Value | 0.458N | 0.536N | 0.699N | 0.091N | 0.382N | 0.499N |
| | RTE P-Value | 0.441N | 0.454 | 0.353 | 0.078N | 0.370 | 0.477 |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|---------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Alimentary System | | | | | | | |
| Liver * Basophilic Focus | Simple Incidence | 1/23 (4.3%) | 0/22 (0.0%) | 0/22 (0.0%) | 5/24 (20.8%) | 0/20 (0.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 1/21 (4.8%) | 0/22 (0.0%) | 0/21 (0.0%) | 5/22 (22.7%) | 0/20 (0.0%) | 1/24 (4.2%) |
| | Time-to-First | 362 (T) | ---- | ---- | 362 (T) | ---- | 361 (T) |
| | CAFE P-Value | 0.332 | 0.511N | 0.511N | 0.104 | 0.535N | 0.745N |
| Liver * Fatty Change | Simple Incidence | 2/23 (8.7%) | 4/22 (18.2%) | 2/22 (9.1%) | 1/24 (4.2%) | 0/20 (0.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/22 (18.2%) | 2/21 (9.5%) | 1/22 (4.5%) | 0/20 (0.0%) | 1/24 (4.2%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) | 361 (T) | ---- | 361 (T) |
| | CAFE P-Value | 0.052N | 0.311 | 0.679 | 0.484N | 0.280N | 0.484N |
| | Severity Profile | 0 1 1 0 | 1 2 1 0 | 1 1 0 0 | 0 1 0 0 | --- | 0 0 1 0 |
| | JT/SW P-Value | 0.042N* | 0.806N | 0.566N | 0.370N | 0.188N | 0.269N |
| RTE P-Value | 0.039N* | 0.122 | 0.495N | 0.268N | 0.097N | 0.278N | |
| Liver * Hepatodiaphragmatic Nodule | Simple Incidence | 2/23 (8.7%) | 2/22 (9.1%) | 1/22 (4.5%) | 2/24 (8.3%) | 1/20 (5.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 2/22 (9.1%) | 1/21 (4.8%) | 2/22 (9.1%) | 1/20 (5.0%) | 0/24 (0.0%) |
| | Time-to-First | 359 (T) | 361 (T) | 363 (T) | 361 (T) | 362 (T) | ---- |
| | CAFE P-Value | 0.124N | 0.679 | 0.517N | 0.679N | 0.554N | 0.234N |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 3/23 (13.0%) | 6/22 (27.3%) | 5/22 (22.7%) | 5/24 (20.8%) | 3/20 (15.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 3/21 (14.3%) | 6/22 (27.3%) | 5/21 (23.8%) | 4/22 (18.2%) | 3/20 (15.0%) | 2/24 (8.3%) |
| | Time-to-First | 362 (T) | 360 (T) | 362 (T) | 322 | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.196N | 0.207 | 0.324 | 0.375 | 0.597 | 0.479N |
| | Severity Profile | 3 0 0 0 | 4 2 0 0 | 3 2 0 0 | 4 1 0 0 | 3 0 0 0 | 1 1 0 0 |
| | JT/SW P-Value | 0.184N | 0.898N | 0.886N | 0.863N | 0.701N | 0.493N |
| RTE P-Value | 0.185N | 0.086 | 0.161 | 0.235 | 0.437 | 0.370N | |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 4/23 (17.4%) | 6/22 (27.3%) | 4/22 (18.2%) | 5/24 (20.8%) | 5/20 (25.0%) | 4/24 (16.7%) |
| | Terminal Incidence | 4/21 (19.0%) | 6/22 (27.3%) | 4/21 (19.0%) | 5/22 (22.7%) | 5/20 (25.0%) | 4/24 (16.7%) |
| | Time-to-First | 362 (T) | 361 (T) | 362 (T) | 361 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.471N | 0.331 | 0.624 | 0.529 | 0.405 | 0.625N |
| | Severity Profile | 4 0 0 0 | 5 1 0 0 | 4 0 0 0 | 5 0 0 0 | 5 0 0 0 | 4 0 0 0 |
| | JT/SW P-Value | 0.432N | 0.802N | 0.610N | 0.694N | 0.759N | 0.621N |
| RTE P-Value | 0.442N | 0.174 | 0.475 | 0.389 | 0.275 | 0.476N | |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Liver * Mixed Cell Focus | Simple Incidence | 0/23 (0.0%) | 0/22 (0.0%) | 0/22 (0.0%) | 2/24 (8.3%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 0/22 (0.0%) | 0/21 (0.0%) | 1/22 (4.5%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Time-to-First | ---- | ---- | ---- | 256 | ---- | ---- |
| | CAFE P-Value | 0.417 | | | 0.255 | | |
| Liver * Tension Lipidosis | Simple Incidence | 3/23 (13.0%) | 3/22 (13.6%) | 2/22 (9.1%) | 2/24 (8.3%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/22 (13.6%) | 2/21 (9.5%) | 2/22 (9.1%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Time-to-First | 307 | 358 (T) | 361 (T) | 362 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.094N | 0.646 | 0.522N | 0.479N | 0.359N | 0.288N |
| | Severity Profile | 0 2 1 0 | 0 1 1 1 | 0 1 0 1 | 0 1 1 0 | 0 0 1 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.078N | 0.554N | 0.431N | 0.399N | 0.272N | 0.188N |
| | RTE P-Value | 0.077N | 0.450 | 0.339N | 0.295N | 0.222N | 0.146N |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 2/23 (8.7%) | 1/22 (4.5%) | 1/22 (4.5%) | 1/24 (4.2%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 2/21 (9.5%) | 1/22 (4.5%) | 1/21 (4.8%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Time-to-First | 360 (T) | 361 (T) | 362 (T) | 363 (T) | 363 (T) | 361 (T) |
| | CAFE P-Value | 0.328N | 0.517N | 0.517N | 0.484N | 0.554N | 0.484N |
| | Severity Profile | 2 0 0 0 | 1 0 0 0 | 1 0 0 0 | 1 0 0 0 | 0 1 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.292N | 0.291N | 0.334N | 0.319N | 0.370N | 0.331N |
| | RTE P-Value | 0.301N | 0.271N | 0.271N | 0.249N | 0.312N | 0.249N |
| Pancreas * Degeneration,Acinus | Simple Incidence | 13/23 (56.5%) | 13/22 (59.1%) | 14/22 (63.6%) | 19/24 (79.2%) | 13/20 (65.0%) | 18/24 (75.0%) |
| | Terminal Incidence | 12/21 (57.1%) | 13/22 (59.1%) | 14/21 (66.7%) | 17/22 (77.3%) | 13/20 (65.0%) | 18/24 (75.0%) |
| | Time-to-First | 56 | 358 (T) | 360 (T) | 256 | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.067 | 0.551 | 0.428 | 0.088 | 0.400 | 0.152 |
| | Severity Profile | 5 5 2 1 | 7 4 1 1 | 7 6 0 1 | 8 7 4 0 | 6 5 1 1 | 5 10 1 2 |
| | JT/SW P-Value | 0.044 * | 0.567 | 0.554 | 0.119 | 0.276 | 0.110 |
| | RTE P-Value | 0.052 | 0.407N | 0.496N | 0.104 | 0.399 | 0.086 |
| Pancreas * Infiltration Cellular,Lymphocyte | Simple Incidence | 0/23 (0.0%) | 2/22 (9.1%) | 0/22 (0.0%) | 0/24 (0.0%) | 1/20 (5.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 2/22 (9.1%) | 0/21 (0.0%) | 0/22 (0.0%) | 1/20 (5.0%) | 0/24 (0.0%) |
| | Time-to-First | ---- | 361 (T) | ---- | ---- | 361 (T) | ---- |
| | CAFE P-Value | 0.374N | 0.233 | | | 0.465 | |
| | Severity Profile | --- | 1 0 1 0 | --- | --- | 1 0 0 0 | --- |
| | JT/SW P-Value | 0.303N | 0.928N | 0.583N | 0.618N | 0.760N | 0.648N |
| | RTE P-Value | 0.314N | 0.007 ** | 0.500 | 0.500 | 0.138 | 0.500 |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|---------------|--------------|--------------|--------------|--------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Cardiovascular System | | | | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 7/23 (30.4%) | 10/22 (45.5%) | 9/22 (40.9%) | 8/24 (33.3%) | 9/20 (45.0%) | 7/24 (29.2%) |
| | Terminal Incidence | 7/21 (33.3%) | 10/22 (45.5%) | 8/21 (38.1%) | 7/22 (31.8%) | 9/20 (45.0%) | 7/24 (29.2%) |
| | Time-to-First | 360 (T) | 358 (T) | 311 | 322 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.431N | 0.233 | 0.337 | 0.540 | 0.252 | 0.588N |
| | Severity Profile | 6 1 0 0 | 8 2 0 0 | 7 2 0 0 | 8 0 0 0 | 8 1 0 0 | 6 1 0 0 |
| | JT/SW P-Value | 0.378N | 0.856N | 0.857N | 0.651N | 0.814N | 0.608N |
| | RTE P-Value | 0.397N | 0.140 | 0.215 | 0.469 | 0.177 | 0.465N |
| Endocrine System | | | | | | | |
| Adrenal Cortex * Degeneration,Cystic | Simple Incidence | 2/23 (8.7%) | 2/22 (9.1%) | 3/22 (13.6%) | 2/24 (8.3%) | 2/20 (10.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 2/21 (9.5%) | 2/22 (9.1%) | 3/21 (14.3%) | 2/22 (9.1%) | 2/20 (10.0%) | 2/24 (8.3%) |
| | Time-to-First | 362 (T) | 360 (T) | 361 (T) | 362 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.497N | 0.679 | 0.478 | 0.679N | 0.641 | 0.679N |
| | Severity Profile | 1 0 1 0 | 0 2 0 0 | 1 1 0 1 | 0 1 0 1 | 0 1 1 0 | 1 0 1 0 |
| | JT/SW P-Value | 0.471N | 0.518N | 0.706N | 0.620N | 0.672N | 0.630N |
| | RTE P-Value | 0.476N | 0.483 | 0.288 | 0.498 | 0.432 | 0.484N |
| Adrenal Cortex * Vacuolization Cytoplasmic | Simple Incidence | 2/23 (8.7%) | 0/22 (0.0%) | 1/22 (4.5%) | 0/24 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 1/21 (4.8%) | 0/22 (0.0%) | 1/21 (4.8%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Time-to-First | 56 | ---- | 363 (T) | ---- | ---- | ---- |
| | CAFE P-Value | 0.045N* | 0.256N | 0.517N | 0.234N | 0.280N | 0.234N |
| | Severity Profile | 0 2 0 0 | --- | 0 1 0 0 | --- | --- | --- |
| | JT/SW P-Value | 0.031N* | 0.081N | 0.180N | 0.059N | 0.050N | 0.027N* |
| | RTE P-Value | 0.037N* | 0.025N* | 0.299N | 0.031N* | 0.017N* | 0.031N* |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 2/23 (8.7%) | 0/21 (0.0%) | 3/20 (15.0%) | 2/23 (8.7%) | 1/20 (5.0%) | 1/23 (4.3%) |
| | Terminal Incidence | 1/21 (4.8%) | 0/21 (0.0%) | 3/20 (15.0%) | 1/21 (4.8%) | 1/20 (5.0%) | 1/23 (4.3%) |
| | Time-to-First | 56 | ---- | 362 (T) | 322 | 363 (T) | 361 (T) |
| | CAFE P-Value | 0.422N | 0.267N | 0.431 | 0.696N | 0.554N | 0.500N |
| | Severity Profile | 2 0 0 0 | --- | 2 1 0 0 | 1 1 0 0 | 1 0 0 0 | 0 1 0 0 |
| | JT/SW P-Value | 0.394N | 0.086N | 0.522N | 0.584N | 0.430N | 0.405N |
| | RTE P-Value | 0.402N | 0.141N | 0.160 | 0.484 | 0.323N | 0.301N |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 2/23 (8.7%) | 0/22 (0.0%) | 0/22 (0.0%) | 2/24 (8.3%) | 1/20 (5.0%) | 2/24 (8.3%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 2/21 (9.5%) | 0/22 (0.0%) | 0/21 (0.0%) | 2/22 (9.1%) | 1/20 (5.0%) | 2/24 (8.3%) |
| | Time-to-First | 360 (T) | ---- | ---- | 362 (T) | 363 (T) | 361 (T) |
| | CAFE P-Value | 0.332 | 0.256N | 0.256N | 0.679N | 0.554N | 0.679N |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 18/23 (78.3%) | 17/22 (77.3%) | 18/22 (81.8%) | 15/24 (62.5%) | 16/20 (80.0%) | 20/24 (83.3%) |
| | Terminal Incidence | 17/21 (81.0%) | 17/22 (77.3%) | 17/21 (81.0%) | 15/22 (68.2%) | 16/20 (80.0%) | 20/24 (83.3%) |
| | Time-to-First | 307 | 356 (T) | 311 | 360 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.448 | 0.609N | 0.530 | 0.195N | 0.595 | 0.471 |
| | Severity Profile | 8 6 3 1 | 7 6 3 1 | 7 4 5 2 | 8 4 2 1 | 8 6 1 1 | 7 8 4 1 |
| | JT/SW P-Value | 0.451 | 0.477 | 0.273 | 0.684 | 0.708 | 0.355 |
| | RTE P-Value | 0.474 | 0.478 | 0.232 | 0.118N | 0.413N | 0.263 |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 14/23 (60.9%) | 11/22 (50.0%) | 15/21 (71.4%) | 12/24 (50.0%) | 8/20 (40.0%) | 16/24 (66.7%) |
| | Terminal Incidence | 14/21 (66.7%) | 11/22 (50.0%) | 15/21 (71.4%) | 11/22 (50.0%) | 8/20 (40.0%) | 16/24 (66.7%) |
| | Time-to-First | 359 (T) | 356 (T) | 360 (T) | 322 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.457N | 0.333N | 0.338 | 0.325N | 0.145N | 0.456 |
| | Severity Profile | 8 6 0 0 | 9 2 0 0 | 12 3 0 0 | 9 3 0 0 | 4 3 1 0 | 12 3 1 0 |
| | JT/SW P-Value | 0.423N | 0.126N | 0.343N | 0.174N | 0.145N | 0.309N |
| | RTE P-Value | 0.408N | 0.126N | 0.443 | 0.140N | 0.114N | 0.492 |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 7/23 (30.4%) | 7/22 (31.8%) | 5/21 (23.8%) | 8/24 (33.3%) | 6/20 (30.0%) | 11/24 (45.8%) |
| | Terminal Incidence | 7/21 (33.3%) | 7/22 (31.8%) | 5/21 (23.8%) | 8/22 (36.4%) | 6/20 (30.0%) | 11/24 (45.8%) |
| | Time-to-First | 361 (T) | 358 (T) | 362 (T) | 361 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.166 | 0.587 | 0.440N | 0.540 | 0.619N | 0.216 |
| Genital System | | | | | | | |
| Ovary * Atrophy | Simple Incidence | 10/23 (43.5%) | 7/22 (31.8%) | 9/22 (40.9%) | 14/24 (58.3%) | 11/20 (55.0%) | 11/24 (45.8%) |
| | Terminal Incidence | 10/21 (47.6%) | 7/22 (31.8%) | 8/21 (38.1%) | 13/22 (59.1%) | 11/20 (55.0%) | 11/24 (45.8%) |
| | Time-to-First | 361 (T) | 356 (T) | 311 | 322 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.153 | 0.309N | 0.551N | 0.234 | 0.327 | 0.552 |
| | Severity Profile | 1 4 0 5 | 0 3 0 4 | 0 2 0 7 | 6 4 0 4 | 2 1 0 8 | 0 2 0 9 |
| | JT/SW P-Value | 0.096 | 0.748 | 0.514 | 0.430 | 0.226 | 0.299 |
| | RTE P-Value | 0.091 | 0.267N | 0.432 | 0.350 | 0.173 | 0.283 |
| Ovary * Cyst | Simple Incidence | 1/23 (4.3%) | 0/22 (0.0%) | 2/22 (9.1%) | 0/24 (0.0%) | 1/20 (5.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 1/21 (4.8%) | 0/22 (0.0%) | 2/21 (9.5%) | 0/22 (0.0%) | 1/20 (5.0%) | 0/24 (0.0%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|----------------|----------------|----------------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Time-to-First | 362 (T) | ---- | 361 (T) | ---- | 362 (T) | ---- |
| | CAFE P-Value | 0.334N | 0.511N | 0.483 | 0.489N | 0.720 | 0.489N |
| Ovary * Cyst,Bursa | Simple Incidence | 0/23 (0.0%) | 0/22 (0.0%) | 3/22 (13.6%) | 2/24 (8.3%) | 1/20 (5.0%) | 3/24 (12.5%) |
| | Terminal Incidence | 0/21 (0.0%) | 0/22 (0.0%) | 3/21 (14.3%) | 2/22 (9.1%) | 1/20 (5.0%) | 3/24 (12.5%) |
| | Time-to-First | ---- | ---- | 361 (T) | 362 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.056 | | 0.109 | 0.255 | 0.465 | 0.125 |
| Ovary * Cyst,Corpus Luteum | Simple Incidence | 0/23 (0.0%) | 0/22 (0.0%) | 0/22 (0.0%) | 0/24 (0.0%) | 2/20 (10.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 0/21 (0.0%) | 0/22 (0.0%) | 0/21 (0.0%) | 0/22 (0.0%) | 2/20 (10.0%) | 1/24 (4.2%) |
| | Time-to-First | ---- | ---- | ---- | ---- | 363 (T) | 364 (T) |
| | CAFE P-Value | 0.047 * | | | | 0.210 | 0.511 |
| Ovary * Cyst,Follicle | Simple Incidence | 8/23 (34.8%) | 4/22 (18.2%) | 10/22 (45.5%) | 5/24 (20.8%) | 10/20 (50.0%) | 11/24 (45.8%) |
| | Terminal Incidence | 8/21 (38.1%) | 4/22 (18.2%) | 9/21 (42.9%) | 5/22 (22.7%) | 10/20 (50.0%) | 11/24 (45.8%) |
| | Time-to-First | 361 (T) | 356 (T) | 311 | 361 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.083 | 0.179N | 0.335 | 0.229N | 0.242 | 0.318 |
| Ovary * Depletion,Corpus Luteum | Simple Incidence | 4/23 (17.4%) | 4/22 (18.2%) | 7/22 (31.8%) | 4/24 (16.7%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 4/21 (19.0%) | 4/22 (18.2%) | 6/21 (28.6%) | 4/22 (18.2%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Time-to-First | 362 (T) | 356 (T) | 311 | 361 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.032 * | 0.624 | 0.219 | 0.625N | 0.095 | 0.112 |
| Ovary * Diestrus | Simple Incidence | 15/23 (65.2%) | 12/22 (54.5%) | 8/22 (36.4%) | 12/24 (50.0%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 14/21 (66.7%) | 12/22 (54.5%) | 8/21 (38.1%) | 10/22 (45.5%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Time-to-First | 56 | 360 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.031N* | 0.335N | 0.050N | 0.224N | 0.089N | 0.053N |
| Ovary * Hypertrophy,Interstitial Cell | Simple Incidence | 4/23 (17.4%) | 4/22 (18.2%) | 6/22 (27.3%) | 3/24 (12.5%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 4/21 (19.0%) | 4/22 (18.2%) | 5/21 (23.8%) | 2/22 (9.1%) | 8/20 (40.0%) | 9/24 (37.5%) |
| | Time-to-First | 362 (T) | 356 (T) | 311 | 322 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.030 * | 0.624 | 0.331 | 0.475N | 0.095 | 0.112 |
| | Severity Profile | 0 4 0 0 | 0 3 1 0 | 0 2 4 0 | 0 0 2 1 | 0 6 2 0 | 1 7 1 0 |
| | JT/SW P-Value | 0.038 * | 0.446 | 0.174 | 0.428 | 0.049 * ¹ | 0.066 |
| | RTE P-Value | 0.031 * | 0.445 | 0.154 | 0.462N | 0.042 * | 0.068 |
| Ovary * Metestrus | Simple Incidence | 3/23 (13.0%) | 3/22 (13.6%) | 4/22 (18.2%) | 6/24 (25.0%) | 1/20 (5.0%) | 5/24 (20.8%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|---------------|----------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 2/21 (9.5%) | 3/22 (13.6%) | 4/21 (19.0%) | 6/22 (27.3%) | 1/20 (5.0%) | 5/24 (20.8%) |
| | Time-to-First | 307 | 361 (T) | 360 (T) | 360 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.373 | 0.646 | 0.474 | 0.253 | 0.359N | 0.375 |
| Ovary * Proestrus | Simple Incidence | 1/23 (4.3%) | 3/22 (13.6%) | 3/22 (13.6%) | 1/24 (4.2%) | 3/20 (15.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 1/21 (4.8%) | 3/22 (13.6%) | 3/21 (14.3%) | 1/22 (4.5%) | 3/20 (15.0%) | 0/24 (0.0%) |
| | Time-to-First | 364 (T) | 360 (T) | 362 (T) | 362 (T) | 361 (T) | ---- |
| | CAFE P-Value | 0.292N | 0.287 | 0.287 | 0.745N | 0.252 | 0.489N |
| Uterus * Apoptosis | Simple Incidence | 2/23 (8.7%) | 1/22 (4.5%) | 4/21 (19.0%) | 5/24 (20.8%) | 5/20 (25.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 2/21 (9.5%) | 1/22 (4.5%) | 4/21 (19.0%) | 5/22 (22.7%) | 5/20 (25.0%) | 9/24 (37.5%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) | 361 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.001 ** | 0.517N | 0.288 | 0.226 | 0.152 | 0.022 * |
| | Severity Profile | 0 0 0 2 | 0 0 0 1 | 0 1 1 2 | 0 1 0 4 | 0 0 3 2 | 0 1 5 3 |
| | JT/SW P-Value | 0.003 ** | 0.709 | 0.181 | 0.147 | 0.112 | 0.013 * |
| | RTE P-Value | 0.003 ** | 0.350N | 0.219 | 0.142 | 0.103 | 0.010 ** |
| Uterus * Cyst,Endometrium | Simple Incidence | 0/23 (0.0%) | 1/22 (4.5%) | 1/21 (4.8%) | 3/24 (12.5%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/22 (4.5%) | 1/21 (4.8%) | 3/22 (13.6%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Time-to-First | ---- | 356 (T) | 363 (T) | 360 (T) | ---- | ---- |
| | CAFE P-Value | 0.496N | 0.489 | 0.477 | 0.125 | | |
| Uterus * Diestrus | Simple Incidence | 10/23 (43.5%) | 12/22 (54.5%) | 6/21 (28.6%) | 11/24 (45.8%) | 8/20 (40.0%) | 5/24 (20.8%) |
| | Terminal Incidence | 9/21 (42.9%) | 12/22 (54.5%) | 6/21 (28.6%) | 9/22 (40.9%) | 8/20 (40.0%) | 5/24 (20.8%) |
| | Time-to-First | 56 | 360 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.052N | 0.329 | 0.239N | 0.552 | 0.532N | 0.088N |
| Uterus * Dilatation,Lumen | Simple Incidence | 0/23 (0.0%) | 1/22 (4.5%) | 2/21 (9.5%) | 2/24 (8.3%) | 1/20 (5.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/22 (4.5%) | 2/21 (9.5%) | 2/22 (9.1%) | 1/20 (5.0%) | 2/24 (8.3%) |
| | Time-to-First | ---- | 360 (T) | 363 (T) | 362 (T) | 363 (T) | 362 (T) |
| | CAFE P-Value | 0.178 | 0.489 | 0.222 | 0.255 | 0.465 | 0.255 |
| | Severity Profile | --- | 0 0 1 0 | 0 0 0 2 | 0 0 0 2 | 0 0 0 1 | 0 0 0 2 |
| | JT/SW P-Value | 0.142 | 0.153 | 0.075 | 0.114 | 0.175 | 0.151 |
| | RTE P-Value | 0.159 | 0.274 | 0.132 | 0.120 | 0.247 | 0.117 |
| Uterus * Estrus | Simple Incidence | 4/23 (17.4%) | 2/22 (9.1%) | 4/21 (19.0%) | 5/24 (20.8%) | 6/20 (30.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 4/21 (19.0%) | 2/22 (9.1%) | 4/21 (19.0%) | 5/22 (22.7%) | 6/20 (30.0%) | 9/24 (37.5%) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|---------------|---------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Time-to-First | 362 (T) | 358 (T) | 361 (T) | 361 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.014 * | 0.354N | 0.596 | 0.529 | 0.269 | 0.112 |
| Uterus * Hyperplasia,Cystic,Endometrium | Simple Incidence | 5/23 (21.7%) | 1/22 (4.5%) | 4/21 (19.0%) | 3/24 (12.5%) | 7/20 (35.0%) | 4/24 (16.7%) |
| | Terminal Incidence | 5/21 (23.8%) | 1/22 (4.5%) | 4/21 (19.0%) | 3/22 (13.6%) | 7/20 (35.0%) | 4/24 (16.7%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) | 361 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.246 | 0.103N | 0.562N | 0.325N | 0.265 | 0.471N |
| | Severity Profile | 1 2 1 1 | 1 0 0 0 | 1 2 1 0 | 1 1 1 0 | 0 6 1 0 | 0 3 0 1 |
| | JT/SW P-Value | 0.212 | 0.960 | 0.706 | 0.855 | 0.180 | 0.519 |
| | RTE P-Value | 0.178 | 0.051N | 0.384N | 0.175N | 0.129 | 0.327N |
| Uterus * Hyperplasia,Endometrium | Simple Incidence | 2/23 (8.7%) | 7/22 (31.8%) | 5/21 (23.8%) | 7/24 (29.2%) | 5/20 (25.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 2/21 (9.5%) | 7/22 (31.8%) | 5/21 (23.8%) | 6/22 (27.3%) | 5/20 (25.0%) | 2/24 (8.3%) |
| | Time-to-First | 362 (T) | 360 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.417N | 0.058 | 0.170 | 0.078 | 0.152 | 0.679N |
| | Severity Profile | 0 2 0 0 | 3 3 1 0 | 0 4 1 0 | 2 4 1 0 | 1 2 2 0 | 0 2 0 0 |
| | JT/SW P-Value | 0.431N | 0.967N | 0.950N | 0.977N | 0.973N | 0.635N |
| | RTE P-Value | 0.437N | 0.042 * | 0.105 | 0.049 * | 0.083 | 0.488N |
| Uterus * Metaplasia,Squamous | Simple Incidence | 1/23 (4.3%) | 1/22 (4.5%) | 4/21 (19.0%) | 3/24 (12.5%) | 3/20 (15.0%) | 5/24 (20.8%) |
| | Terminal Incidence | 1/21 (4.8%) | 1/22 (4.5%) | 4/21 (19.0%) | 3/22 (13.6%) | 3/20 (15.0%) | 5/24 (20.8%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) | 361 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.037 * | 0.744 | 0.145 | 0.321 | 0.252 | 0.104 |
| | Severity Profile | 0 1 0 0 | 0 1 0 0 | 3 1 0 0 | 3 0 0 0 | 2 0 1 0 | 5 0 0 0 |
| | JT/SW P-Value | 0.041 * | 0.487 | 0.063 | 0.144 | 0.178 | 0.073 |
| | RTE P-Value | 0.044 * | 0.491 | 0.093 | 0.226 | 0.165 | 0.065 |
| Uterus * Metestrus | Simple Incidence | 7/23 (30.4%) | 4/22 (18.2%) | 7/21 (33.3%) | 7/24 (29.2%) | 2/20 (10.0%) | 8/24 (33.3%) |
| | Terminal Incidence | 6/21 (28.6%) | 4/22 (18.2%) | 7/21 (33.3%) | 7/22 (31.8%) | 2/20 (10.0%) | 8/24 (33.3%) |
| | Time-to-First | 307 | 356 (T) | 360 (T) | 360 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.488N | 0.272N | 0.546 | 0.588N | 0.101N | 0.540 |
| Uterus * Proestrus | Simple Incidence | 2/23 (8.7%) | 4/22 (18.2%) | 3/21 (14.3%) | 1/24 (4.2%) | 4/20 (20.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/22 (18.2%) | 3/21 (14.3%) | 1/22 (4.5%) | 4/20 (20.0%) | 2/24 (8.3%) |
| | Time-to-First | 364 (T) | 360 (T) | 360 (T) | 362 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.462N | 0.311 | 0.455 | 0.484N | 0.266 | 0.679N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|---------------|--------------|---------------|--------------|--------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Vagina * Diestrus | Simple Incidence | 11/23 (47.8%) | 11/22 (50.0%) | 7/21 (33.3%) | 10/24 (41.7%) | 9/20 (45.0%) | 7/24 (29.2%) |
| | Terminal Incidence | 10/21 (47.6%) | 11/22 (50.0%) | 7/21 (33.3%) | 9/22 (40.9%) | 9/20 (45.0%) | 7/24 (29.2%) |
| | Time-to-First | 56 | 360 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.124N | 0.560 | 0.252N | 0.448N | 0.548N | 0.155N |
| Vagina * Estrus | Simple Incidence | 3/23 (13.0%) | 2/22 (9.1%) | 3/21 (14.3%) | 5/24 (20.8%) | 7/20 (35.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 3/21 (14.3%) | 2/22 (9.1%) | 3/21 (14.3%) | 5/22 (22.7%) | 7/20 (35.0%) | 9/24 (37.5%) |
| | Time-to-First | 362 (T) | 358 (T) | 363 (T) | 361 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.003 ** | 0.522N | 0.622 | 0.375 | 0.090 | 0.055 |
| Vagina * Hyperplasia,Epithelium | Simple Incidence | 3/23 (13.0%) | 2/22 (9.1%) | 2/21 (9.5%) | 4/24 (16.7%) | 6/20 (30.0%) | 8/24 (33.3%) |
| | Terminal Incidence | 3/21 (14.3%) | 2/22 (9.1%) | 2/21 (9.5%) | 4/22 (18.2%) | 6/20 (30.0%) | 8/24 (33.3%) |
| | Time-to-First | 362 (T) | 358 (T) | 363 (T) | 361 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.008 ** | 0.522N | 0.545N | 0.525 | 0.162 | 0.097 |
| | Severity Profile | 0 1 2 0 | 0 1 1 0 | 0 1 1 0 | 0 0 4 0 | 0 1 5 0 | 0 1 7 0 |
| | JT/SW P-Value | 0.005 ** | 0.669 | 0.742 | 0.418 | 0.074 | 0.041 * |
| | RTE P-Value | 0.005 ** | 0.360N | 0.375N | 0.343 | 0.067 | 0.030 * |
| Vagina * Metestrus | Simple Incidence | 7/23 (30.4%) | 5/22 (22.7%) | 8/21 (38.1%) | 8/24 (33.3%) | 2/20 (10.0%) | 8/24 (33.3%) |
| | Terminal Incidence | 6/21 (28.6%) | 5/22 (22.7%) | 8/21 (38.1%) | 7/22 (31.8%) | 2/20 (10.0%) | 8/24 (33.3%) |
| | Time-to-First | 307 | 356 (T) | 360 (T) | 322 | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.422N | 0.403N | 0.414 | 0.540 | 0.101N | 0.540 |
| Vagina * Mucification,Epithelium | Simple Incidence | 10/23 (43.5%) | 12/22 (54.5%) | 7/21 (33.3%) | 9/24 (37.5%) | 7/20 (35.0%) | 8/24 (33.3%) |
| | Terminal Incidence | 10/21 (47.6%) | 12/22 (54.5%) | 7/21 (33.3%) | 8/22 (36.4%) | 7/20 (35.0%) | 8/24 (33.3%) |
| | Time-to-First | 360 (T) | 358 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.123N | 0.329 | 0.353N | 0.452N | 0.400N | 0.339N |
| | Severity Profile | 0 6 1 3 | 0 7 4 1 | 0 0 3 4 | 0 1 5 3 | 0 0 2 5 | 1 3 1 3 |
| | JT/SW P-Value | 0.272N | 0.720N | 0.552N | 0.607N | 0.638N | 0.385N |
| | RTE P-Value | 0.256N | 0.317 | 0.447N | 0.482N | 0.471 | 0.288N |
| Vagina * Proestrus | Simple Incidence | 2/23 (8.7%) | 4/22 (18.2%) | 2/21 (9.5%) | 1/24 (4.2%) | 2/20 (10.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/22 (18.2%) | 2/21 (9.5%) | 1/22 (4.5%) | 2/20 (10.0%) | 0/24 (0.0%) |
| | Time-to-First | 364 (T) | 360 (T) | 362 (T) | 362 (T) | 361 (T) | ---- |
| | CAFE P-Value | 0.072N | 0.311 | 0.661 | 0.484N | 0.641 | 0.234N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|----------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Hematopoietic System | | | | | | | |
| Spleen * Hematopoietic Cell Proliferation | Simple Incidence | 3/23 (13.0%) | 3/22 (13.6%) | 2/22 (9.1%) | 3/24 (12.5%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/22 (13.6%) | 1/21 (4.8%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/24 (4.2%) |
| | Time-to-First | 56 | 356 (T) | 311 | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.118N | 0.646 | 0.522N | 0.646N | 0.359N | 0.288N |
| | Severity Profile | 1 2 0 0 | 0 2 1 0 | 2 0 0 0 | 1 0 1 1 | 0 1 0 0 | 0 1 0 0 |
| | JT/SW P-Value | 0.107N | 0.561N | 0.381N | 0.523N | 0.276N | 0.215N |
| | RTE P-Value | 0.111N | 0.447 | 0.314N | 0.498 | 0.222N | 0.191N |
| Spleen * Pigmentation | Simple Incidence | 22/23 (95.7%) | 21/22 (95.5%) | 20/22 (90.9%) | 24/24 (100.0%) | 19/20 (95.0%) | 23/24 (95.8%) |
| | Terminal Incidence | 21/21 (100.0%) | 21/22 (95.5%) | 19/21 (90.5%) | 22/22 (100.0%) | 19/20 (95.0%) | 23/24 (95.8%) |
| | Time-to-First | 307 | 356 (T) | 311 | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.451 | 0.744N | 0.483N | 0.489 | 0.720N | 0.745 |
| | Severity Profile | 0 8 10 4 | 4 6 8 3 | 2 4 9 5 | 1 7 11 5 | 0 6 8 5 | 1 5 12 5 |
| | JT/SW P-Value | 0.123 | 0.851 | 0.601 | 0.430 | 0.439 | 0.421 |
| | RTE P-Value | 0.115 | 0.166N | 0.493 | 0.339 | 0.331 | 0.314 |
| Thymus * Atrophy | Simple Incidence | 20/23 (87.0%) | 20/22 (90.9%) | 18/22 (81.8%) | 21/24 (87.5%) | 16/20 (80.0%) | 22/24 (91.7%) |
| | Terminal Incidence | 19/21 (90.5%) | 20/22 (90.9%) | 18/21 (85.7%) | 20/22 (90.9%) | 16/20 (80.0%) | 22/24 (91.7%) |
| | Time-to-First | 56 | 356 (T) | 360 (T) | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.525 | 0.522 | 0.474N | 0.646 | 0.418N | 0.479 |
| | Severity Profile | 0 2 8 10 | 1 4 7 8 | 0 6 8 4 | 2 3 7 9 | 0 4 5 7 | 0 5 10 7 |
| | JT/SW P-Value | 0.263N | 0.282N | 0.035N* ¹ | 0.131N | 0.170N | 0.187N |
| | RTE P-Value | 0.260N | 0.287N | 0.036N* | 0.243N | 0.156N | 0.237N |
| Integumentary System | | | | | | | |
| Mammary Gland * Atypical Focus | Simple Incidence | 0/23 (0.0%) | 3/22 (13.6%) | 2/22 (9.1%) | 2/24 (8.3%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 3/22 (13.6%) | 2/21 (9.5%) | 2/22 (9.1%) | 0/20 (0.0%) | 0/24 (0.0%) |
| | Time-to-First | ---- | 358 (T) | 362 (T) | 362 (T) | ---- | ---- |
| | CAFE P-Value | 0.186N | 0.109 | 0.233 | 0.255 | | |
| | Severity Profile | --- | 1 2 0 0 | 0 2 0 0 | 2 0 0 0 | --- | --- |
| | JT/SW P-Value | 0.149N | 0.965N | 0.934N | 0.931N | 0.636N | 0.648N |
| | RTE P-Value | 0.133N | 0.017 * | 0.057 | 0.134 | 0.500 | 0.500 |
| Mammary Gland * Dilatation,Duct | Simple Incidence | 2/23 (8.7%) | 2/22 (9.1%) | 7/22 (31.8%) | 1/24 (4.2%) | 2/20 (10.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 2/21 (9.5%) | 2/22 (9.1%) | 6/21 (28.6%) | 1/22 (4.5%) | 2/20 (10.0%) | 2/24 (8.3%) |

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Time-to-First | 362 (T) | 358 (T) | 311 | 362 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.348N | 0.679 | 0.058 | 0.484N | 0.641 | 0.679N |
| | Severity Profile | 1 1 0 0 | 0 0 0 2 | 2 4 1 0 | 0 0 1 0 | 1 0 1 0 | 1 0 1 0 |
| | JT/SW P-Value | 0.308N | 0.555N | 0.927N | 0.447N | 0.576N | 0.604N |
| | RTE P-Value | 0.312N | 0.428 | 0.010 ** | 0.338N | 0.436 | 0.497N |
| Mammary Gland * Hyperplasia,Lobular | Simple Incidence | 10/23 (43.5%) | 14/22 (63.6%) | 13/22 (59.1%) | 15/24 (62.5%) | 13/20 (65.0%) | 12/24 (50.0%) |
| | Terminal Incidence | 10/21 (47.6%) | 14/22 (63.6%) | 12/21 (57.1%) | 14/22 (63.6%) | 13/20 (65.0%) | 12/24 (50.0%) |
| | Time-to-First | 361 (T) | 356 (T) | 311 | 256 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.355 | 0.145 | 0.227 | 0.155 | 0.135 | 0.438 |
| | Severity Profile | 5 5 0 0 | 7 7 0 0 | 7 6 0 0 | 11 3 1 0 | 10 2 0 1 | 9 1 1 1 |
| | JT/SW P-Value | 0.421N | 0.894N | 0.886N | 0.889N | 0.904N | 0.700N |
| | RTE P-Value | 0.444N | 0.099 | 0.174 | 0.205 | 0.196 | 0.452 |
| Urinary System | | | | | | | |
| Kidney * Casts Protein | Simple Incidence | 2/23 (8.7%) | 4/22 (18.2%) | 2/22 (9.1%) | 4/24 (16.7%) | 3/20 (15.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 1/21 (4.8%) | 4/22 (18.2%) | 2/21 (9.5%) | 4/22 (18.2%) | 3/20 (15.0%) | 1/24 (4.2%) |
| | Time-to-First | 307 | 361 (T) | 360 (T) | 361 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.348N | 0.311 | 0.679 | 0.354 | 0.431 | 0.484N |
| | Severity Profile | 2 0 0 0 | 4 0 0 0 | 2 0 0 0 | 4 0 0 0 | 3 0 0 0 | 0 1 0 0 |
| | JT/SW P-Value | 0.341N | 0.823N | 0.601N | 0.790N | 0.818N | 0.452N |
| | RTE P-Value | 0.351N | 0.168 | 0.484 | 0.204 | 0.266 | 0.338N |
| Kidney * Cyst,Cortex | Simple Incidence | 2/23 (8.7%) | 2/22 (9.1%) | 2/22 (9.1%) | 4/24 (16.7%) | 3/20 (15.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 2/21 (9.5%) | 2/22 (9.1%) | 2/21 (9.5%) | 3/22 (13.6%) | 3/20 (15.0%) | 2/24 (8.3%) |
| | Time-to-First | 362 (T) | 360 (T) | 362 (T) | 322 | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.380 | 0.679 | 0.679 | 0.354 | 0.431 | 0.679N |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 0/23 (0.0%) | 7/22 (31.8%) | 3/22 (13.6%) | 3/24 (12.5%) | 3/20 (15.0%) | 1/24 (4.2%) |
| | Terminal Incidence | 0/21 (0.0%) | 7/22 (31.8%) | 3/21 (14.3%) | 3/22 (13.6%) | 3/20 (15.0%) | 1/24 (4.2%) |
| | Time-to-First | ---- | 356 (T) | 361 (T) | 361 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.324N | 0.004 ** | 0.109 | 0.125 | 0.092 | 0.511 |
| Kidney * Mineralization | Simple Incidence | 11/23 (47.8%) | 5/22 (22.7%) | 11/22 (50.0%) | 12/24 (50.0%) | 11/20 (55.0%) | 16/24 (66.7%) |
| | Terminal Incidence | 10/21 (47.6%) | 5/22 (22.7%) | 10/21 (47.6%) | 11/22 (50.0%) | 11/20 (55.0%) | 16/24 (66.7%) |
| | Time-to-First | 307 | 360 (T) | 311 | 256 | 361 (T) | 361 (T) |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 9 Nonneoplasms by Body System for Interim Sacrifice Females Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|--------------|----------------------|--------------|---------------|--------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | CAFE P-Value | 0.017 * | 0.073N | 0.560 | 0.557 | 0.435 | 0.156 |
| | Severity Profile | 11 0 0 0 | 3 1 1 0 | 7 2 1 1 | 11 1 0 0 | 8 3 0 0 | 10 3 3 0 |
| | JT/SW P-Value | 0.006 ** | 0.923 | 0.319 | 0.416 | 0.274 | 0.035 * |
| | RTE P-Value | 0.006 ** | 0.124N | 0.232 | 0.401 | 0.204 | 0.025 * |
| Kidney * Nephropathy | Simple Incidence | 6/23 (26.1%) | 7/22 (31.8%) | 11/22 (50.0%) | 8/24 (33.3%) | 11/20 (55.0%) | 7/24 (29.2%) |
| | Terminal Incidence | 5/21 (23.8%) | 7/22 (31.8%) | 10/21 (47.6%) | 7/22 (31.8%) | 11/20 (55.0%) | 7/24 (29.2%) |
| | Time-to-First | 56 | 356 (T) | 311 | 322 | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.258 | 0.462 | 0.089 | 0.412 | 0.052 | 0.536 |
| | Severity Profile | 4 1 0 1 | 5 1 1 0 | 6 2 0 3 | 6 1 0 1 | 9 0 2 0 | 3 2 1 1 |
| | JT/SW P-Value | 0.236 | 0.355 | 0.045 * ¹ | 0.171 | 0.057 | 0.196 |
| | RTE P-Value | 0.213 | 0.372 | 0.036 * | 0.334 | 0.048 * | 0.356 |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.

Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm

| System and Nonneoplasm | Lesion | Statistic | Treatment (ug/kg) | | | | |
|------------------------------------|--------------------|---------------|-------------------|---------------|---------------|---------------|--------------|
| | | | Control | 2.5 | 25 | 250 | 2500 |
| Alimentary System | | | | | | | |
| Liver * Basophilic Focus | Simple Incidence | 1/22 (4.5%) | 0/22 (0.0%) | 3/20 (15.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/18 (5.6%) | 0/22 (0.0%) | 3/18 (16.7%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 363 (T) | ---- | 360 (T) | ---- | ---- | ---- |
| | CAFE P-Value | 0.162N | 0.500N | 0.267 | 0.478N | 0.537N | 0.500N |
| Liver * Clear Cell Focus | Simple Incidence | 3/22 (13.6%) | 1/22 (4.5%) | 0/20 (0.0%) | 1/24 (4.2%) | 0/19 (0.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 3/18 (16.7%) | 1/22 (4.5%) | 0/18 (0.0%) | 1/24 (4.2%) | 0/18 (0.0%) | 1/21 (4.8%) |
| | Time-to-First | 361 (T) | 362 (T) | ---- | 361 (T) | ---- | 362 (T) |
| | CAFE P-Value | 0.097N | 0.303N | 0.134N | 0.271N | 0.144N | 0.303N |
| Liver * Degeneration,Cystic | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 1/20 (5.0%) | 0/24 (0.0%) | 1/19 (5.3%) | 0/22 (0.0%) |
| | Terminal Incidence | 2/18 (11.1%) | 0/22 (0.0%) | 1/18 (5.6%) | 0/24 (0.0%) | 1/18 (5.6%) | 0/21 (0.0%) |
| | Time-to-First | 362 (T) | ---- | 361 (T) | ---- | 360 (T) | ---- |
| | CAFE P-Value | 0.162N | 0.244N | 0.537N | 0.223N | 0.556N | 0.244N |
| | Severity Profile | 2 0 0 | --- | 1 0 0 | --- | 1 0 0 | --- |
| | JT/SW P-Value | 0.122N | 0.076N | 0.184N | 0.056N | 0.169N | 0.053N |
| RTE P-Value | 0.147N | 0.037N* | 0.224N | 0.036N* | 0.242N | 0.037N* | |
| Liver * Eosinophilic Focus | Simple Incidence | 1/22 (4.5%) | 0/22 (0.0%) | 1/20 (5.0%) | 1/24 (4.2%) | 2/19 (10.5%) | 1/22 (4.5%) |
| | Terminal Incidence | 1/18 (5.6%) | 0/22 (0.0%) | 1/18 (5.6%) | 1/24 (4.2%) | 2/18 (11.1%) | 1/21 (4.8%) |
| | Time-to-First | 361 (T) | ---- | 361 (T) | 362 (T) | 360 (T) | 362 (T) |
| | CAFE P-Value | 0.266 | 0.500N | 0.732 | 0.733N | 0.444 | 0.756 |
| Liver * Fatty Change | Simple Incidence | 0/22 (0.0%) | 0/22 (0.0%) | 2/20 (10.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 2/18 (11.1%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | ---- | ---- | 359 (T) | ---- | ---- | ---- |
| | CAFE P-Value | 0.423N | ---- | 0.221 | ---- | ---- | ---- |
| | Severity Profile | --- | --- | 0 2 0 | --- | --- | --- |
| | JT/SW P-Value | 0.342N | 0.500N | 0.882N | 0.618N | 0.636N | 0.648N |
| RTE P-Value | 0.324N | 0.500 | 0.012 * | 0.500 | 0.500 | 0.500 | |
| Liver * Hepatodiaphragmatic Nodule | Simple Incidence | 0/22 (0.0%) | 2/22 (9.1%) | 2/20 (10.0%) | 3/24 (12.5%) | 4/19 (21.1%) | 1/22 (4.5%) |
| | Terminal Incidence | 0/18 (0.0%) | 2/22 (9.1%) | 1/18 (5.6%) | 3/24 (12.5%) | 3/18 (16.7%) | 1/21 (4.8%) |
| | Time-to-First | ---- | 362 (T) | 319 | 360 (T) | 244 | 362 (T) |
| | CAFE P-Value | 0.158 | 0.244 | 0.221 | 0.133 | 0.038 * | 0.500 |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|----------------------|---------------|----------------|----------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 3/22 (13.6%) | 6/22 (27.3%) | 2/20 (10.0%) | 6/24 (25.0%) | 5/19 (26.3%) | 1/22 (4.5%) |
| | Terminal Incidence | 2/18 (11.1%) | 6/22 (27.3%) | 2/18 (11.1%) | 6/24 (25.0%) | 5/18 (27.8%) | 1/21 (4.8%) |
| | Time-to-First | 258 | 360 (T) | 361 (T) | 359 (T) | 360 (T) | 362 (T) |
| | CAFE P-Value | 0.318N | 0.228 | 0.547N | 0.277 | 0.265 | 0.303N |
| | Severity Profile | 2 0 1 0 | 3 3 0 0 | 2 0 0 0 | 5 1 0 0 | 4 1 0 0 | 0 1 0 0 |
| | JT/SW P-Value | 0.286N | 0.865N | 0.421N | 0.743N | 0.819N | 0.303N |
| | RTE P-Value | 0.300N | 0.101 | 0.354N | 0.183 | 0.163 | 0.223N |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 5/22 (22.7%) | 11/22 (50.0%) | 9/20 (45.0%) | 13/24 (54.2%) | 11/19 (57.9%) | 8/22 (36.4%) |
| | Terminal Incidence | 5/18 (27.8%) | 11/22 (50.0%) | 9/18 (50.0%) | 13/24 (54.2%) | 11/18 (61.1%) | 8/21 (38.1%) |
| | Time-to-First | 361 (T) | 360 (T) | 359 (T) | 359 (T) | 360 (T) | 359 (T) |
| | CAFE P-Value | 0.149 | 0.058 | 0.115 | 0.029 * | 0.023 * | 0.255 |
| | Severity Profile | 5 0 0 0 | 11 0 0 0 | 9 0 0 0 | 12 1 0 0 | 11 0 0 0 | 8 0 0 0 |
| | JT/SW P-Value | 0.130 | 0.032 * ¹ | 0.059 | 0.015 * | 0.016 * | 0.046 * |
| | RTE P-Value | 0.128 | 0.034 * | 0.080 | 0.012 * | 0.015 * | 0.165 |
| Liver * Tension Lipidosis | Simple Incidence | 1/22 (4.5%) | 0/22 (0.0%) | 3/20 (15.0%) | 3/24 (12.5%) | 2/19 (10.5%) | 1/22 (4.5%) |
| | Terminal Incidence | 1/18 (5.6%) | 0/22 (0.0%) | 3/18 (16.7%) | 3/24 (12.5%) | 2/18 (11.1%) | 1/21 (4.8%) |
| | Time-to-First | 362 (T) | ---- | 361 (T) | 362 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.305 | 0.500N | 0.267 | 0.338 | 0.444 | 0.756 |
| | Severity Profile | 0 1 0 0 | --- | 0 2 0 1 | 0 1 2 0 | 1 1 0 0 | 0 0 1 0 |
| | JT/SW P-Value | 0.270 | 0.841 | 0.094 | 0.156 | 0.228 | 0.302 |
| | RTE P-Value | 0.274 | 0.292N | 0.083 | 0.139 | 0.254 | 0.486 |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 8/22 (36.4%) | 1/22 (4.5%) | 6/20 (30.0%) | 11/24 (45.8%) | 8/19 (42.1%) | 8/22 (36.4%) |
| | Terminal Incidence | 8/18 (44.4%) | 1/22 (4.5%) | 6/18 (33.3%) | 11/24 (45.8%) | 8/18 (44.4%) | 8/21 (38.1%) |
| | Time-to-First | 359 (T) | 362 (T) | 361 (T) | 360 (T) | 360 (T) | 361 (T) |
| | CAFE P-Value | 0.073 | 0.011N* | 0.457N | 0.363 | 0.478 | 0.623N |
| | Severity Profile | 6 2 0 0 | 1 0 0 0 | 4 2 0 0 | 6 5 0 0 | 6 2 0 0 | 4 4 0 0 |
| | JT/SW P-Value | 0.050 | 0.995 | 0.755 | 0.245 | 0.352 | 0.419 |
| | RTE P-Value | 0.046 * | 0.014N* | 0.356N | 0.191 | 0.353 | 0.417 |
| Pancreas * Basophilic Focus | Simple Incidence | 0/22 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 2/24 (8.3%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 2/24 (8.3%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | ---- | ---- | ---- | 362 (T) | ---- | ---- |
| | CAFE P-Value | 0.410 | | | 0.267 | | |

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|----------------------|----------------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Pancreas * Degeneration,Acinus | Simple Incidence | 19/22 (86.4%) | 21/22 (95.5%) | 17/20 (85.0%) | 23/24 (95.8%) | 16/19 (84.2%) | 19/22 (86.4%) |
| | Terminal Incidence | 17/18 (94.4%) | 21/22 (95.5%) | 16/18 (88.9%) | 23/24 (95.8%) | 15/18 (83.3%) | 19/21 (90.5%) |
| | Time-to-First | 173 | 356 (T) | 127 | 359 (T) | 244 | 359 (T) |
| | CAFE P-Value | 0.386N | 0.303 | 0.620N | 0.271 | 0.594N | 0.668N |
| | Severity Profile | 4 4 5 6 | 3 9 7 2 | 8 6 3 0 | 6 10 5 2 | 1 8 6 1 | 5 3 8 3 |
| | JT/SW P-Value | 0.358N | 0.386N | 0.010N* ¹ | 0.067N | 0.133N | 0.184N |
| | RTE P-Value | 0.362N | 0.452N | 0.007N** | 0.190N | 0.267N | 0.329N |
| Pancreas * Pigmentation | Simple Incidence | 8/22 (36.4%) | 7/22 (31.8%) | 10/20 (50.0%) | 13/24 (54.2%) | 7/19 (36.8%) | 11/22 (50.0%) |
| | Terminal Incidence | 7/18 (38.9%) | 7/22 (31.8%) | 10/18 (55.6%) | 13/24 (54.2%) | 7/18 (38.9%) | 11/21 (52.4%) |
| | Time-to-First | 258 | 356 (T) | 359 (T) | 359 (T) | 360 (T) | 361 (T) |
| | CAFE P-Value | 0.161 | 0.500N | 0.281 | 0.180 | 0.614 | 0.272 |
| | Severity Profile | 6 2 0 0 | 5 2 0 0 | 9 1 0 0 | 13 0 0 0 | 6 1 0 0 | 8 3 0 0 |
| | JT/SW P-Value | 0.164 | 0.611 | 0.286 | 0.250 | 0.400 | 0.229 |
| | RTE P-Value | 0.176 | 0.393N | 0.246 | 0.203 | 0.470N | 0.178 |
| Cardiovascular System | | | | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 16/22 (72.7%) | 16/22 (72.7%) | 16/20 (80.0%) | 18/24 (75.0%) | 15/20 (75.0%) | 20/22 (90.9%) |
| | Terminal Incidence | 14/18 (77.8%) | 16/22 (72.7%) | 15/18 (83.3%) | 18/24 (75.0%) | 14/18 (77.8%) | 20/21 (95.2%) |
| | Time-to-First | 258 | 356 (T) | 319 | 360 (T) | 300 | 359 (T) |
| | CAFE P-Value | 0.116 | 0.632N | 0.426 | 0.563 | 0.574 | 0.120 |
| | Severity Profile | 11 4 1 0 | 11 3 2 0 | 11 5 0 0 | 11 4 2 1 | 14 1 0 0 | 15 4 0 1 |
| | JT/SW P-Value | 0.326 | 0.475 | 0.422 | 0.383 | 0.596 | 0.240 |
| | RTE P-Value | 0.352 | 0.477 | 0.346 | 0.297 | 0.231N | 0.178 |
| Endocrine System | | | | | | | |
| Adrenal Cortex * Vacuolization Cytoplasmic | Simple Incidence | 0/22 (0.0%) | 3/22 (13.6%) | 1/20 (5.0%) | 2/24 (8.3%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 0/18 (0.0%) | 3/22 (13.6%) | 1/18 (5.6%) | 2/24 (8.3%) | 0/18 (0.0%) | 2/21 (9.5%) |
| | Time-to-First | ---- | 361 (T) | 362 (T) | 362 (T) | ---- | 362 (T) |
| | CAFE P-Value | 0.453 | 0.116 | 0.476 | 0.267 | 0.244 | 0.244 |
| | Severity Profile | --- | 0 3 0 0 | 0 1 0 0 | 1 1 0 0 | --- | 1 0 1 0 |
| | JT/SW P-Value | 0.416 | 0.038 * ¹ | 0.122 | 0.142 | 0.216 | 0.139 |
| | RTE P-Value | 0.431 | 0.031 * | 0.250 | 0.141 | 0.500 | 0.109 |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 7/22 (31.8%) | 5/21 (23.8%) | 7/19 (36.8%) | 5/24 (20.8%) | 2/19 (10.5%) | 2/21 (9.5%) |

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|---------------|--------------|---------------|--------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 7/18 (38.9%) | 5/21 (23.8%) | 7/17 (41.2%) | 5/24 (20.8%) | 2/17 (11.8%) | 2/21 (9.5%) |
| | Time-to-First | 361 (T) | 356 (T) | 360 (T) | 359 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.018N* | 0.404N | 0.496 | 0.305N | 0.102N | 0.076N |
| | Severity Profile | 3 4 0 0 | 2 3 0 0 | 3 3 1 0 | 1 4 0 0 | 0 2 0 0 | 1 1 0 0 |
| | JT/SW P-Value | 0.019N* | 0.289N | 0.547N | 0.309N | 0.097N | 0.055N |
| | RTE P-Value | 0.019N* | 0.273N | 0.333 | 0.216N | 0.064N | 0.045N* |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 1/22 (4.5%) | 0/22 (0.0%) | 0/20 (0.0%) | 3/24 (12.5%) | 1/20 (5.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/18 (5.6%) | 0/22 (0.0%) | 0/18 (0.0%) | 3/24 (12.5%) | 1/18 (5.6%) | 2/21 (9.5%) |
| | Time-to-First | 361 (T) | ---- | ---- | 362 (T) | 362 (T) | 359 (T) |
| | CAFE P-Value | 0.129 | 0.500N | 0.524N | 0.338 | 0.732 | 0.500 |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 4/22 (18.2%) | 6/22 (27.3%) | 2/20 (10.0%) | 4/24 (16.7%) | 2/20 (10.0%) | 4/22 (18.2%) |
| | Terminal Incidence | 4/18 (22.2%) | 6/22 (27.3%) | 2/18 (11.1%) | 4/24 (16.7%) | 2/18 (11.1%) | 4/21 (19.0%) |
| | Time-to-First | 359 (T) | 361 (T) | 362 (T) | 359 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.279N | 0.360 | 0.380N | 0.598N | 0.380N | 0.651 |
| | Severity Profile | 3 1 0 0 | 6 0 0 0 | 1 1 0 0 | 2 2 0 0 | 2 0 0 0 | 2 2 0 0 |
| | JT/SW P-Value | 0.288N | 0.730N | 0.311N | 0.464N | 0.303N | 0.493N |
| | RTE P-Value | 0.287N | 0.246 | 0.256N | 0.472N | 0.234N | 0.473 |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 10/22 (45.5%) | 13/22 (59.1%) | 9/20 (45.0%) | 12/24 (50.0%) | 7/18 (38.9%) | 10/21 (47.6%) |
| | Terminal Incidence | 8/18 (44.4%) | 13/22 (59.1%) | 9/18 (50.0%) | 12/24 (50.0%) | 7/18 (38.9%) | 10/21 (47.6%) |
| | Time-to-First | 173 | 356 (T) | 360 (T) | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.344N | 0.273 | 0.610N | 0.495 | 0.462N | 0.565 |
| | Severity Profile | 3 4 3 0 | 7 4 2 0 | 6 2 1 0 | 5 4 3 0 | 2 4 0 1 | 6 3 1 0 |
| | JT/SW P-Value | 0.263N | 0.652N | 0.343N | 0.529N | 0.422N | 0.457N |
| | RTE P-Value | 0.263N | 0.327 | 0.294N | 0.448 | 0.321N | 0.368N |
| Thyroid Gland * Hyperplasia,Follicular Cell | Simple Incidence | 1/22 (4.5%) | 1/22 (4.5%) | 2/20 (10.0%) | 2/24 (8.3%) | 2/18 (11.1%) | 1/21 (4.8%) |
| | Terminal Incidence | 1/18 (5.6%) | 1/22 (4.5%) | 2/18 (11.1%) | 2/24 (8.3%) | 2/18 (11.1%) | 1/21 (4.8%) |
| | Time-to-First | 359 (T) | 360 (T) | 361 (T) | 362 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.385 | 0.756 | 0.463 | 0.533 | 0.423 | 0.744 |
| | Severity Profile | 0 1 0 0 | 0 0 1 0 | 1 0 1 0 | 0 1 1 0 | 0 0 2 0 | 0 0 1 0 |
| | JT/SW P-Value | 0.324 | 0.487 | 0.281 | 0.343 | 0.267 | 0.407 |
| | RTE P-Value | 0.329 | 0.486 | 0.251 | 0.307 | 0.174 | 0.475 |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 5/22 (22.7%) | 4/22 (18.2%) | 6/20 (30.0%) | 5/24 (20.8%) | 5/18 (27.8%) | 7/21 (33.3%) |

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------------|----------------|----------------------|----------------------|---------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Terminal Incidence | 5/18 (27.8%) | 4/22 (18.2%) | 6/18 (33.3%) | 5/24 (20.8%) | 5/18 (27.8%) | 7/21 (33.3%) |
| | Time-to-First | 353 (T) | 361 (T) | 359 (T) | 359 (T) | 360 (T) | 361 (T) |
| | CAFE P-Value | 0.198 | 0.500N | 0.426 | 0.578N | 0.497 | 0.332 |
| Genital System | | | | | | | |
| Epididymis * Exfoliated Germ Cell | Simple Incidence | 1/22 (4.5%) | 1/22 (4.5%) | 1/20 (5.0%) | 1/24 (4.2%) | 0/20 (0.0%) | 6/22 (27.3%) |
| | Terminal Incidence | 1/18 (5.6%) | 1/22 (4.5%) | 1/18 (5.6%) | 1/24 (4.2%) | 0/18 (0.0%) | 6/21 (28.6%) |
| | Time-to-First | 362 (T) | 362 (T) | 362 (T) | 362 (T) | ---- | 360 (T) |
| | CAFE P-Value | 0.021 * | 0.756 | 0.732 | 0.733N | 0.524N | 0.047 * |
| | Severity Profile | 1 0 0 0 | 1 0 0 0 | 0 1 0 0 | 1 0 0 0 | --- | 6 0 0 0 |
| | JT/SW P-Value | 0.018 * | 0.500 | 0.538 | 0.610 | 0.709 | 0.003 ** |
| | RTE P-Value | 0.019 * | 0.500 | 0.458 | 0.480N | 0.286N | 0.002 ** |
| Epididymis * Hypospermia | Simple Incidence | 2/22 (9.1%) | 4/22 (18.2%) | 1/20 (5.0%) | 2/24 (8.3%) | 0/20 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 1/18 (5.6%) | 4/22 (18.2%) | 1/18 (5.6%) | 2/24 (8.3%) | 0/18 (0.0%) | 2/21 (9.5%) |
| | Time-to-First | 258 | 361 (T) | 362 (T) | 362 (T) | ---- | 361 (T) |
| | CAFE P-Value | 0.186N | 0.332 | 0.537N | 0.662N | 0.268N | 0.697N |
| | Severity Profile | 0 0 1 1 | 0 0 0 4 | 0 0 0 1 | 0 0 0 2 | --- | 0 0 0 2 |
| | JT/SW P-Value | 0.170N | 0.828N | 0.420N | 0.526N | 0.201N | 0.429N |
| | RTE P-Value | 0.168N | 0.088 | 0.333N | 0.482N | 0.151N | 0.482 |
| Epididymis * Infiltration Cellular,Lymphocyte | Simple Incidence | 0/22 (0.0%) | 1/22 (4.5%) | 3/20 (15.0%) | 2/24 (8.3%) | 0/20 (0.0%) | 5/22 (22.7%) |
| | Terminal Incidence | 0/18 (0.0%) | 1/22 (4.5%) | 3/18 (16.7%) | 2/24 (8.3%) | 0/18 (0.0%) | 5/21 (23.8%) |
| | Time-to-First | ---- | 362 (T) | 360 (T) | 362 (T) | ---- | 361 (T) |
| | CAFE P-Value | 0.032 * | 0.500 | 0.099 | 0.267 | ---- | 0.024 * |
| | Severity Profile | --- | 0 1 0 0 | 3 0 0 0 | 2 0 0 0 | --- | 5 0 0 0 |
| | JT/SW P-Value | 0.030 * | 0.159 | 0.029 * ¹ | 0.083 | 0.182 | 0.004 ** |
| | RTE P-Value | 0.034 * | 0.276 | 0.050 | 0.120 | 0.500 | 0.006 ** |
| Prostate, Dorsal/Lateral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 4/22 (18.2%) | 10/22 (45.5%) | 5/20 (25.0%) | 6/24 (25.0%) | 5/20 (25.0%) | 7/22 (31.8%) |
| | Terminal Incidence | 4/18 (22.2%) | 10/22 (45.5%) | 5/18 (27.8%) | 6/24 (25.0%) | 5/18 (27.8%) | 7/21 (33.3%) |
| | Time-to-First | 361 (T) | 356 (T) | 362 (T) | 360 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.487 | 0.052 | 0.435 | 0.422 | 0.435 | 0.244 |
| | Severity Profile | 4 0 0 0 | 9 1 0 0 | 5 0 0 0 | 5 1 0 0 | 5 0 0 0 | 5 2 0 0 |
| | JT/SW P-Value | 0.413 | 0.025 * ¹ | 0.123 | 0.185 | 0.246 | 0.167 |
| | RTE P-Value | 0.419 | 0.025 * | 0.320 | 0.282 | 0.320 | 0.126 |

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|----------------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| Prostate, Dorsal/Lateral Lobe * Inflammation,Suppurative | Simple Incidence | 18/22 (81.8%) | 20/22 (90.9%) | 18/20 (90.0%) | 22/24 (91.7%) | 18/20 (90.0%) | 19/22 (86.4%) |
| | Terminal Incidence | 17/18 (94.4%) | 20/22 (90.9%) | 16/18 (88.9%) | 22/24 (91.7%) | 17/18 (94.4%) | 19/21 (90.5%) |
| | Time-to-First | 258 | 356 (T) | 127 | 359 (T) | 300 | 359 (T) |
| | CAFE P-Value | 0.383 | 0.332 | 0.380 | 0.291 | 0.380 | 0.500 |
| | Severity Profile | 11 7 0 0 | 6 14 0 0 | 9 9 0 0 | 9 12 1 0 | 6 10 2 0 | 7 11 1 0 |
| | JT/SW P-Value | 0.076 | 0.022 * ¹ | 0.077 | 0.053 | 0.025 * | 0.048 * |
| | RTE P-Value | 0.074 | 0.025 * | 0.175 | 0.048 * | 0.022 * | 0.063 |
| Prostate, Ventral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 8/22 (36.4%) | 10/22 (45.5%) | 10/20 (50.0%) | 8/24 (33.3%) | 9/20 (45.0%) | 8/22 (36.4%) |
| | Terminal Incidence | 7/18 (38.9%) | 10/22 (45.5%) | 9/18 (50.0%) | 8/24 (33.3%) | 8/18 (44.4%) | 8/21 (38.1%) |
| | Time-to-First | 173 | 360 (T) | 127 | 360 (T) | 244 | 360 (T) |
| | CAFE P-Value | 0.434N | 0.380 | 0.281 | 0.537N | 0.399 | 0.623N |
| | Severity Profile | 8 0 0 0 | 8 2 0 0 | 9 1 0 0 | 7 1 0 0 | 8 1 0 0 | 7 1 0 0 |
| | JT/SW P-Value | 0.437N | 0.793N | 0.883N | 0.582N | 0.745N | 0.701N |
| | RTE P-Value | 0.442N | 0.209 | 0.162 | 0.468N | 0.256 | 0.452 |
| Prostate, Ventral Lobe * Inflammation,Suppurative | Simple Incidence | 10/22 (45.5%) | 3/22 (13.6%) | 4/20 (20.0%) | 5/24 (20.8%) | 3/20 (15.0%) | 1/22 (4.5%) |
| | Terminal Incidence | 10/18 (55.6%) | 3/22 (13.6%) | 4/18 (22.2%) | 5/24 (20.8%) | 3/18 (16.7%) | 1/21 (4.8%) |
| | Time-to-First | 353 (T) | 361 (T) | 361 (T) | 362 (T) | 360 (T) | 363 (T) |
| | CAFE P-Value | 0.003N** | 0.023N* | 0.077N | 0.071N | 0.035N* | 0.002N** |
| | Severity Profile | 9 1 0 0 | 3 0 0 0 | 2 2 0 0 | 4 1 0 0 | 3 0 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.003N** | 0.010N* | 0.027N* | 0.026N* | 0.012N* | <.001N*** |
| | RTE P-Value | 0.003N** | 0.005N** | 0.027N* | 0.021N* | 0.009N** | <.001N*** |
| Testes * Degeneration,Seminiferous Tubule | Simple Incidence | 6/22 (27.3%) | 7/22 (31.8%) | 9/20 (45.0%) | 10/24 (41.7%) | 5/20 (25.0%) | 9/22 (40.9%) |
| | Terminal Incidence | 4/18 (22.2%) | 7/22 (31.8%) | 9/18 (50.0%) | 10/24 (41.7%) | 5/18 (27.8%) | 9/21 (42.9%) |
| | Time-to-First | 258 | 361 (T) | 360 (T) | 359 (T) | 360 (T) | 360 (T) |
| | CAFE P-Value | 0.303 | 0.500 | 0.191 | 0.238 | 0.574N | 0.263 |
| | Severity Profile | 3 1 0 2 | 3 0 0 4 | 7 1 0 1 | 8 0 0 2 | 5 0 0 0 | 3 4 0 2 |
| | JT/SW P-Value | 0.326 | 0.336 | 0.216 | 0.252 | 0.428 | 0.198 |
| | RTE P-Value | 0.347 | 0.335 | 0.184 | 0.227 | 0.328N | 0.152 |
| Hematopoietic System | | | | | | | |
| Spleen * Hematopoietic Cell Proliferation | Simple Incidence | 0/22 (0.0%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 2/22 (9.1%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 1/21 (4.8%) |

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Statistic</i> | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> | |
| | Time-to-First | ---- | ---- | ---- | ---- | ---- | 28 |
| | CAFE P-Value | 0.028 * | | | | | 0.244 |
| | Severity Profile | --- | --- | --- | --- | --- | 0 2 0 0 |
| | JT/SW P-Value | 0.019 * | 0.500 | 0.583 | 0.618 | 0.636 | 0.009 ** |
| | RTE P-Value | 0.013 * | 0.500 | 0.500 | 0.500 | 0.500 | 0.013 * |
| Spleen * Pigmentation | | | | | | | |
| | Simple Incidence | 15/22 (68.2%) | 16/22 (72.7%) | 15/20 (75.0%) | 16/24 (66.7%) | 15/18 (83.3%) | 13/22 (59.1%) |
| | Terminal Incidence | 14/18 (77.8%) | 16/22 (72.7%) | 14/18 (77.8%) | 16/24 (66.7%) | 15/18 (83.3%) | 13/21 (61.9%) |
| | Time-to-First | 173 | 356 (T) | 319 | 360 (T) | 360 (T) | 359 (T) |
| | CAFE P-Value | 0.382N | 0.500 | 0.443 | 0.582N | 0.233 | 0.377N |
| | Severity Profile | 6 7 1 1 | 7 9 0 0 | 2 10 3 0 | 7 9 0 0 | 2 13 0 0 | 6 6 1 0 |
| | JT/SW P-Value | 0.397N | 0.475N | 0.786N | 0.414N | 0.775N | 0.288N |
| | RTE P-Value | 0.433N | 0.451N | 0.094 | 0.320N | 0.082 | 0.211N |
| Thymus * Atrophy | | | | | | | |
| | Simple Incidence | 18/22 (81.8%) | 21/22 (95.5%) | 17/20 (85.0%) | 22/24 (91.7%) | 17/19 (89.5%) | 20/21 (95.2%) |
| | Terminal Incidence | 18/18 (100.0%) | 21/22 (95.5%) | 16/18 (88.9%) | 22/24 (91.7%) | 17/18 (94.4%) | 20/20 (100.0%) |
| | Time-to-First | 353 (T) | 356 (T) | 319 | 359 (T) | 360 (T) | 359 (T) |
| | CAFE P-Value | 0.176 | 0.172 | 0.556 | 0.291 | 0.406 | 0.187 |
| | Severity Profile | 2 1 1 14 | 0 2 5 14 | 1 0 2 14 | 1 4 6 11 | 0 1 6 10 | 0 1 5 14 |
| | JT/SW P-Value | 0.454 | 0.288 | 0.351 | 0.546 | 0.595 | 0.288 |
| | RTE P-Value | 0.458 | 0.282 | 0.278 | 0.241N | 0.456N | 0.215 |
| Integumentary System | | | | | | | |
| Mammary Gland * Hyperplasia,Lobular | | | | | | | |
| | Simple Incidence | 2/22 (9.1%) | 1/21 (4.8%) | 0/20 (0.0%) | 3/24 (12.5%) | 1/19 (5.3%) | 0/22 (0.0%) |
| | Terminal Incidence | 2/18 (11.1%) | 1/21 (4.8%) | 0/18 (0.0%) | 3/24 (12.5%) | 1/17 (5.9%) | 0/21 (0.0%) |
| | Time-to-First | 361 (T) | 361 (T) | ---- | 362 (T) | 362 (T) | ---- |
| | CAFE P-Value | 0.257N | 0.518N | 0.268N | 0.543 | 0.556N | 0.244N |
| | Severity Profile | 0 2 0 0 | 1 0 0 0 | --- | 1 1 1 0 | 0 1 0 0 | --- |
| | JT/SW P-Value | 0.224N | 0.273N | 0.097N | 0.433N | 0.410N | 0.121N |
| | RTE P-Value | 0.226N | 0.256N | 0.076N | 0.307 | 0.295N | 0.083N |
| Urinary System | | | | | | | |
| Kidney * Accumulation, Hyaline Droplet | | | | | | | |
| | Simple Incidence | 2/22 (9.1%) | 0/22 (0.0%) | 0/20 (0.0%) | 0/24 (0.0%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/18 (0.0%) | 0/24 (0.0%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 282 | ---- | ---- | ---- | ---- | ---- |
| | CAFE P-Value | 0.028N* | 0.244N | 0.268N | 0.223N | 0.282N | 0.244N |

Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice)

| <i>Table 10. Nonneoplasms by Body System for Interim Sacrifice Males Bisphenol-A Continuous Dose Arm</i> | | | | | | | |
|--|--------------------|--------------------------|----------------|----------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>2.5</i> | <i>25</i> | <i>250</i> | <i>2500</i> | <i>25000</i> |
| | Severity Profile | 0 0 0 2 | --- | --- | --- | --- | --- |
| | JT/SW P-Value | 0.019N* | 0.076N | 0.054N | 0.024N* | 0.020N* | 0.009N** |
| | RTE P-Value | 0.013N* | 0.013N* | 0.013N* | 0.013N* | 0.013N* | 0.013N* |
| Kidney * Casts Protein | Simple Incidence | 2/22 (9.1%) | 1/22 (4.5%) | 0/20 (0.0%) | 1/24 (4.2%) | 0/19 (0.0%) | 0/22 (0.0%) |
| | Terminal Incidence | 1/18 (5.6%) | 1/22 (4.5%) | 0/18 (0.0%) | 1/24 (4.2%) | 0/18 (0.0%) | 0/21 (0.0%) |
| | Time-to-First | 258 | 361 (T) | ---- | 363 (T) | ---- | ---- |
| | CAFE P-Value | 0.055N | 0.500N | 0.268N | 0.467N | 0.282N | 0.244N |
| | Severity Profile | 1 1 0 0 | 1 0 0 0 | --- | 1 0 0 0 | --- | --- |
| | JT/SW P-Value | 0.039N* | 0.268N | 0.097N | 0.166N | 0.079N | 0.051N |
| | RTE P-Value | 0.035N* | 0.130N | 0.043N* | 0.102N | 0.046N* | 0.047N* |
| Kidney * Cyst,Cortex | Simple Incidence | 4/22 (18.2%) | 7/22 (31.8%) | 6/20 (30.0%) | 2/24 (8.3%) | 4/19 (21.1%) | 5/22 (22.7%) |
| | Terminal Incidence | 4/18 (22.2%) | 7/22 (31.8%) | 5/18 (27.8%) | 2/24 (8.3%) | 4/18 (22.2%) | 5/21 (23.8%) |
| | Time-to-First | 361 (T) | 360 (T) | 319 | 359 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.357N | 0.244 | 0.296 | 0.291N | 0.562 | 0.500 |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 4/22 (18.2%) | 6/22 (27.3%) | 9/20 (45.0%) | 7/24 (29.2%) | 4/19 (21.1%) | 7/22 (31.8%) |
| | Terminal Incidence | 4/18 (22.2%) | 6/22 (27.3%) | 8/18 (44.4%) | 7/24 (29.2%) | 4/18 (22.2%) | 7/21 (33.3%) |
| | Time-to-First | 362 (T) | 360 (T) | 127 | 359 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.337 | 0.360 | 0.061 | 0.301 | 0.562 | 0.244 |
| Kidney * Nephropathy | Simple Incidence | 16/22 (72.7%) | 20/22 (90.9%) | 18/20 (90.0%) | 19/24 (79.2%) | 16/19 (84.2%) | 17/22 (77.3%) |
| | Terminal Incidence | 15/18 (83.3%) | 20/22 (90.9%) | 17/18 (94.4%) | 19/24 (79.2%) | 16/18 (88.9%) | 17/21 (81.0%) |
| | Time-to-First | 173 | 356 (T) | 127 | 359 (T) | 360 (T) | 359 (T) |
| | CAFE P-Value | 0.476N | 0.120 | 0.152 | 0.434 | 0.308 | 0.500 |
| | Severity Profile | 9 5 2 0 | 12 7 1 0 | 10 6 2 0 | 10 7 2 0 | 8 7 0 1 | 11 6 0 0 |
| | JT/SW P-Value | 0.392N | 0.801N | 0.893N | 0.812N | 0.863N | 0.544N |
| | RTE P-Value | 0.396N | 0.205 | 0.148 | 0.306 | 0.204 | 0.411N |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Alimentary System | | | | |
| Liver * Basophilic Focus | Simple Incidence | 1/23 (4.3%) | 3/26 (11.5%) | 3/26 (11.5%) |
| | Terminal Incidence | 1/21 (4.8%) | 3/24 (12.5%) | 3/26 (11.5%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.279 | 0.353 | 0.353 |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 3/23 (13.0%) | 8/26 (30.8%) | 4/26 (15.4%) |
| | Terminal Incidence | 3/21 (14.3%) | 8/24 (33.3%) | 4/26 (15.4%) |
| | Time-to-First | 362 (T) | 360 (T) | 361 (T) |
| | CAFE P-Value | 0.515 | 0.127 | 0.571 |
| | Severity Profile | 3 0 0 0 | 6 2 0 0 | 2 2 0 0 |
| | JT/SW P-Value | 0.401 | 0.061 | 0.204 |
| | RTE P-Value | 0.373 | 0.057 | 0.373 |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 4/23 (17.4%) | 7/26 (26.9%) | 2/26 (7.7%) |
| | Terminal Incidence | 4/21 (19.0%) | 7/24 (29.2%) | 2/26 (7.7%) |
| | Time-to-First | 362 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.225N | 0.326 | 0.276N |
| | Severity Profile | 4 0 0 0 | 7 0 0 0 | 2 0 0 0 |
| | JT/SW P-Value | 0.165N | 0.785N | 0.224N |
| | RTE P-Value | 0.220N | 0.217 | 0.220N |
| Liver * Tension Lipidosis | Simple Incidence | 3/23 (13.0%) | 3/26 (11.5%) | 0/26 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/24 (12.5%) | 0/26 (0.0%) |
| | Time-to-First | 307 | 362 (T) | ---- |
| | CAFE P-Value | 0.076N | 0.605N | 0.096N |
| | Severity Profile | 0 2 1 0 | 1 1 0 1 | --- |
| | JT/SW P-Value | 0.043N* | 0.430N | 0.055N |
| | RTE P-Value | 0.059N | 0.418N | 0.059N |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 2/23 (8.7%) | 2/26 (7.7%) | 1/26 (3.8%) |
| | Terminal Incidence | 2/21 (9.5%) | 2/24 (8.3%) | 1/26 (3.8%) |
| | Time-to-First | 360 (T) | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.347N | 0.647N | 0.453N |
| | Severity Profile | 2 0 0 0 | 2 0 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.246N | 0.450N | 0.299N |

| Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm | | | | |
|--|--------------------------|----------------|----------------|----------------|
| System and Nonneoplasm | Treatment (ug/kg) | | | |
| Lesion | Statistic | Control | 0.05 | 0.50 |
| | RTE P-Value | 0.253N | 0.445N | 0.253N |
| Pancreas * Basophilic Focus | Simple Incidence | 0/23 (0.0%) | 2/26 (7.7%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/24 (4.2%) | 0/26 (0.0%) |
| | Time-to-First | ---- | 257 | ---- |
| | CAFE P-Value | 0.639N | 0.276 | |
| Pancreas * Degeneration,Acinus | Simple Incidence | 13/23 (56.5%) | 20/26 (76.9%) | 18/26 (69.2%) |
| | Terminal Incidence | 12/21 (57.1%) | 18/24 (75.0%) | 18/26 (69.2%) |
| | Time-to-First | 56 | 257 | 360 (T) |
| | CAFE P-Value | 0.227 | 0.112 | 0.266 |
| | Severity Profile | 5 5 2 1 | 9 10 1 0 | 10 5 1 2 |
| | JT/SW P-Value | 0.390 | 0.204 | 0.320 |
| | RTE P-Value | 0.364 | 0.194 | 0.364 |
| Cardiovascular System | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 7/23 (30.4%) | 8/26 (30.8%) | 17/26 (65.4%) |
| | Terminal Incidence | 7/21 (33.3%) | 8/24 (33.3%) | 17/26 (65.4%) |
| | Time-to-First | 360 (T) | 360 (T) | 360 (T) |
| | CAFE P-Value | 0.009 ** | 0.613 | 0.015 * |
| | Severity Profile | 6 1 0 0 | 8 0 0 0 | 13 4 0 0 |
| | JT/SW P-Value | 0.004 ** | 0.530 | 0.006 ** |
| | RTE P-Value | 0.004 ** | 0.456N | 0.004 ** |
| Endocrine System | | | | |
| Adrenal Cortex * Degeneration,Cystic | Simple Incidence | 2/23 (8.7%) | 0/26 (0.0%) | 6/26 (23.1%) |
| | Terminal Incidence | 2/21 (9.5%) | 0/24 (0.0%) | 6/26 (23.1%) |
| | Time-to-First | 362 (T) | ---- | 360 (T) |
| | CAFE P-Value | 0.071 | 0.215N | 0.166 |
| | Severity Profile | 1 0 1 0 | --- | 1 4 1 0 |
| | JT/SW P-Value | 0.042 * | 0.936 | 0.062 |
| | RTE P-Value | 0.056 | 0.173N | 0.056 |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 2/23 (8.7%) | 2/26 (7.7%) | 1/25 (4.0%) |
| | Terminal Incidence | 1/21 (4.8%) | 2/24 (8.3%) | 1/25 (4.0%) |
| | Time-to-First | 56 | 361 (T) | 363 (T) |

| Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm | | | | |
|--|--------------------|--------------------------|----------------|----------------|
| System and Nonneoplasm | | Treatment (ug/kg) | | |
| Lesion | Statistic | Control | 0.05 | 0.50 |
| | CAFE P-Value | 0.360N | 0.647N | 0.468N |
| | Severity Profile | 2 0 0 0 | 0 2 0 0 | 1 0 0 0 |
| | JT/SW P-Value | 0.265N | 0.483N | 0.318N |
| | RTE P-Value | 0.269N | 0.475N | 0.269N |
| Pituitary Gland * Angiectasis | Simple Incidence | 1/23 (4.3%) | 2/25 (8.0%) | 6/26 (23.1%) |
| | Terminal Incidence | 1/21 (4.8%) | 2/23 (8.7%) | 6/26 (23.1%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.034 * | 0.532 | 0.069 |
| | Severity Profile | 0 1 0 0 | 0 1 0 1 | 0 4 1 1 |
| | JT/SW P-Value | 0.022 * | 0.294 | 0.026 * |
| | RTE P-Value | 0.025 * | 0.333 | 0.025 * |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 2/23 (8.7%) | 0/25 (0.0%) | 4/26 (15.4%) |
| | Terminal Incidence | 2/21 (9.5%) | 0/23 (0.0%) | 4/26 (15.4%) |
| | Time-to-First | 360 (T) | ---- | 361 (T) |
| | CAFE P-Value | 0.261 | 0.224N | 0.395 |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 18/23 (78.3%) | 20/25 (80.0%) | 25/26 (96.2%) |
| | Terminal Incidence | 17/21 (81.0%) | 20/23 (87.0%) | 25/26 (96.2%) |
| | Time-to-First | 307 | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.057 | 0.581 | 0.070 |
| | Severity Profile | 8 6 3 1 | 10 7 3 0 | 4 11 6 4 |
| | JT/SW P-Value | 0.002 ** | 0.598 | 0.003 ** |
| | RTE P-Value | 0.003 ** | 0.370N | 0.003 ** |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 14/23 (60.9%) | 11/26 (42.3%) | 13/26 (50.0%) |
| | Terminal Incidence | 14/21 (66.7%) | 11/24 (45.8%) | 13/26 (50.0%) |
| | Time-to-First | 359 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.283N | 0.156N | 0.318N |
| | Severity Profile | 8 6 0 0 | 7 4 0 0 | 11 1 1 0 |
| | JT/SW P-Value | 0.139N | 0.094N | 0.122N |
| | RTE P-Value | 0.126N | 0.087N | 0.126N |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 7/23 (30.4%) | 7/26 (26.9%) | 11/26 (42.3%) |
| | Terminal Incidence | 7/21 (33.3%) | 7/24 (29.2%) | 11/26 (42.3%) |
| | Time-to-First | 361 (T) | 361 (T) | 360 (T) |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | CAFE P-Value | 0.226 | 0.517N | 0.287 |
| Genital System | | | | |
| Ovary * Atrophy | Simple Incidence | 10/23 (43.5%) | 9/25 (36.0%) | 26/26 (100.0%) |
| | Terminal Incidence | 10/21 (47.6%) | 9/24 (37.5%) | 26/26 (100.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.407N | <.001 *** |
| | Severity Profile | 1 4 0 5 | 0 3 0 6 | 0 0 0 26 |
| | JT/SW P-Value | <.001 *** | 0.616 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.426N | <.001 *** |
| Ovary * Cyst | Simple Incidence | 1/23 (4.3%) | 1/25 (4.0%) | 2/26 (7.7%) |
| | Terminal Incidence | 1/21 (4.8%) | 1/24 (4.2%) | 2/26 (7.7%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.421 | 0.734N | 0.547 |
| Ovary * Cyst,Bursa | Simple Incidence | 0/23 (0.0%) | 1/25 (4.0%) | 4/26 (15.4%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/24 (4.2%) | 4/26 (15.4%) |
| | Time-to-First | ---- | 363 (T) | 360 (T) |
| | CAFE P-Value | 0.027 * | 0.521 | 0.071 |
| Ovary * Cyst,Follicle | Simple Incidence | 8/23 (34.8%) | 9/25 (36.0%) | 26/26 (100.0%) |
| | Terminal Incidence | 8/21 (38.1%) | 9/24 (37.5%) | 26/26 (100.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.585 | <.001 *** |
| Ovary * Depletion,Corpus Luteum | Simple Incidence | 4/23 (17.4%) | 6/25 (24.0%) | 26/26 (100.0%) |
| | Terminal Incidence | 4/21 (19.0%) | 6/24 (25.0%) | 26/26 (100.0%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.419 | <.001 *** |
| Ovary * Diestrus | Simple Incidence | 15/23 (65.2%) | 12/25 (48.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 14/21 (66.7%) | 11/24 (45.8%) | 0/26 (0.0%) |
| | Time-to-First | 56 | 257 | ---- |
| | CAFE P-Value | <.001N*** | 0.182N | <.001N*** |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|--------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Ovary * Hypertrophy,Interstitial Cell | Simple Incidence | 4/23 (17.4%) | 5/25 (20.0%) | 26/26 (100.0%) |
| | Terminal Incidence | 4/21 (19.0%) | 5/24 (20.8%) | 26/26 (100.0%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.556 | <.001 *** |
| | Severity Profile | 0 4 0 0 | 0 4 1 0 | 1 13 10 2 |
| | JT/SW P-Value | <.001 *** | 0.386 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.339 | <.001 *** |
| Ovary * Metestrus | Simple Incidence | 3/23 (13.0%) | 6/25 (24.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 6/24 (25.0%) | 0/26 (0.0%) |
| | Time-to-First | 307 | 361 (T) | ---- |
| | CAFE P-Value | 0.107N | 0.276 | 0.096N |
| Uterus * Apoptosis | Simple Incidence | 2/23 (8.7%) | 6/25 (24.0%) | 18/26 (69.2%) |
| | Terminal Incidence | 2/21 (9.5%) | 6/24 (25.0%) | 18/26 (69.2%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.151 | <.001 *** |
| | Severity Profile | 0 0 0 2 | 0 1 2 3 | 0 2 6 10 |
| | JT/SW P-Value | <.001 *** | 0.096 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.141 | <.001 *** |
| Uterus * Cyst,Endometrium | Simple Incidence | 0/23 (0.0%) | 2/25 (8.0%) | 2/26 (7.7%) |
| | Terminal Incidence | 0/21 (0.0%) | 2/24 (8.3%) | 2/26 (7.7%) |
| | Time-to-First | ---- | 362 (T) | 362 (T) |
| | CAFE P-Value | 0.206 | 0.266 | 0.276 |
| Uterus * Diestrus | Simple Incidence | 10/23 (43.5%) | 8/25 (32.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 9/21 (42.9%) | 8/24 (33.3%) | 0/26 (0.0%) |
| | Time-to-First | 56 | 360 (T) | ---- |
| | CAFE P-Value | <.001N*** | 0.301N | <.001N*** |
| Uterus * Estrus | Simple Incidence | 4/23 (17.4%) | 6/25 (24.0%) | 21/26 (80.8%) |
| | Terminal Incidence | 4/21 (19.0%) | 6/24 (25.0%) | 21/26 (80.8%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.419 | <.001 *** |
| Uterus * Hyperplasia,Cystic,Endometrium | Simple Incidence | 5/23 (21.7%) | 6/25 (24.0%) | 14/26 (53.8%) |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|---------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Terminal Incidence | 5/21 (23.8%) | 6/24 (25.0%) | 14/26 (53.8%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.012 * | 0.563 | 0.021 * |
| | Severity Profile | 1 2 1 1 | 3 3 0 0 | 4 6 2 2 |
| | JT/SW P-Value | 0.008 ** | 0.511 | 0.013 * |
| | RTE P-Value | 0.012 * | 0.452N | 0.012 * |
| Uterus * Hyperplasia,Endometrial Glands | Simple Incidence | 0/23 (0.0%) | 1/25 (4.0%) | 2/26 (7.7%) |
| | Terminal Incidence | 0/21 (0.0%) | 1/24 (4.2%) | 2/26 (7.7%) |
| | Time-to-First | ---- | 363 (T) | 361 (T) |
| | CAFE P-Value | 0.165 | 0.521 | 0.276 |
| | Severity Profile | --- | 0 1 0 0 | 1 1 0 0 |
| | JT/SW P-Value | 0.091 | 0.169 | 0.106 |
| | RTE P-Value | 0.125 | 0.241 | 0.125 |
| Uterus * Hyperplasia,Endometrium | Simple Incidence | 2/23 (8.7%) | 4/25 (16.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/24 (16.7%) | 0/26 (0.0%) |
| | Time-to-First | 362 (T) | 361 (T) | ---- |
| | CAFE P-Value | 0.185N | 0.375 | 0.215N |
| | Severity Profile | 0 2 0 0 | 0 4 0 0 | --- |
| | JT/SW P-Value | 0.116N | 0.775N | 0.160N |
| | RTE P-Value | 0.174N | 0.232 | 0.174N |
| Uterus * Metaplasia,Squamous | Simple Incidence | 1/23 (4.3%) | 2/25 (8.0%) | 14/26 (53.8%) |
| | Terminal Incidence | 1/21 (4.8%) | 2/24 (8.3%) | 14/26 (53.8%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | <.001 *** | 0.532 | <.001 *** |
| | Severity Profile | 0 1 0 0 | 1 0 1 0 | 8 4 2 0 |
| | JT/SW P-Value | <.001 *** | 0.303 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.367 | <.001 *** |
| Uterus * Metestrus | Simple Incidence | 7/23 (30.4%) | 9/25 (36.0%) | 5/26 (19.2%) |
| | Terminal Incidence | 6/21 (28.6%) | 8/24 (33.3%) | 5/26 (19.2%) |
| | Time-to-First | 307 | 257 | 362 (T) |
| | CAFE P-Value | 0.230N | 0.460 | 0.282N |
| Uterus * Proestrus | Simple Incidence | 2/23 (8.7%) | 2/25 (8.0%) | 0/26 (0.0%) |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Terminal Incidence | 2/21 (9.5%) | 2/24 (8.3%) | 0/26 (0.0%) |
| | Time-to-First | 364 (T) | 362 (T) | ---- |
| | CAFE P-Value | 0.152N | 0.663N | 0.215N |
| Vagina * Diestrus | Simple Incidence | 11/23 (47.8%) | 10/25 (40.0%) | 0/26 (0.0%) |
| | Terminal Incidence | 10/21 (47.6%) | 10/24 (41.7%) | 0/26 (0.0%) |
| | Time-to-First | 56 | 360 (T) | ---- |
| | CAFE P-Value | <.001N*** | 0.399N | <.001N*** |
| Vagina * Estrus | Simple Incidence | 3/23 (13.0%) | 6/25 (24.0%) | 20/26 (76.9%) |
| | Terminal Incidence | 3/21 (14.3%) | 6/24 (25.0%) | 20/26 (76.9%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.276 | <.001 *** |
| Vagina * Hyperplasia,Epithelium | Simple Incidence | 3/23 (13.0%) | 7/25 (28.0%) | 20/26 (76.9%) |
| | Terminal Incidence | 3/21 (14.3%) | 7/24 (29.2%) | 20/26 (76.9%) |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | <.001 *** | 0.180 | <.001 *** |
| | Severity Profile | 0 1 2 0 | 0 4 3 0 | 0 9 11 0 |
| | JT/SW P-Value | <.001 *** | 0.119 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.150 | <.001 *** |
| Vagina * Metestrus | Simple Incidence | 7/23 (30.4%) | 8/25 (32.0%) | 6/26 (23.1%) |
| | Terminal Incidence | 6/21 (28.6%) | 7/24 (29.2%) | 6/26 (23.1%) |
| | Time-to-First | 307 | 257 | 361 (T) |
| | CAFE P-Value | 0.335N | 0.578 | 0.397N |
| Vagina * Mucification,Epithelium | Simple Incidence | 10/23 (43.5%) | 15/25 (60.0%) | 18/26 (69.2%) |
| | Terminal Incidence | 10/21 (47.6%) | 15/24 (62.5%) | 18/26 (69.2%) |
| | Time-to-First | 360 (T) | 360 (T) | 360 (T) |
| | CAFE P-Value | 0.048 * | 0.196 | 0.063 |
| | Severity Profile | 0 6 1 3 | 0 5 1 9 | 1 4 6 7 |
| | JT/SW P-Value | 0.030 * | 0.059 | 0.028 * |
| | RTE P-Value | 0.027 * | 0.052 | 0.027 * |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Hematopoietic System | | | | |
| Spleen * Pigmentation | Simple Incidence | 22/23 (95.7%) | 26/26 (100.0%) | 26/26 (100.0%) |
| | Terminal Incidence | 21/21 (100.0%) | 24/24 (100.0%) | 26/26 (100.0%) |
| | Time-to-First | 307 | 257 | 360 (T) |
| | CAFE P-Value | 0.307 | 0.469 | 0.469 |
| | Severity Profile | 0 8 10 4 | 0 10 11 5 | 0 2 10 14 |
| | JT/SW P-Value | <.001 *** | 0.415 | <.001 *** |
| | RTE P-Value | 0.001 ** | 0.418 | 0.001 ** |
| Thymus * Atrophy | Simple Incidence | 20/23 (87.0%) | 20/25 (80.0%) | 24/26 (92.3%) |
| | Terminal Incidence | 19/21 (90.5%) | 20/23 (87.0%) | 24/26 (92.3%) |
| | Time-to-First | 56 | 360 (T) | 360 (T) |
| | CAFE P-Value | 0.354 | 0.400N | 0.440 |
| | Severity Profile | 0 2 8 10 | 0 5 6 9 | 0 6 2 16 |
| | JT/SW P-Value | 0.232 | 0.830 | 0.297 |
| | RTE P-Value | 0.249 | 0.180N | 0.249 |
| Integumentary System | | | | |
| Mammary Gland * Dilatation,Duct | Simple Incidence | 2/23 (8.7%) | 3/26 (11.5%) | 22/26 (84.6%) |
| | Terminal Incidence | 2/21 (9.5%) | 3/24 (12.5%) | 22/26 (84.6%) |
| | Time-to-First | 362 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.560 | <.001 *** |
| | Severity Profile | 1 1 0 0 | 1 2 0 0 | 6 12 2 2 |
| | JT/SW P-Value | <.001 *** | 0.366 | <.001 *** |
| | RTE P-Value | <.001 *** | 0.373 | <.001 *** |
| Mammary Gland * Galactocele | Simple Incidence | 0/23 (0.0%) | 0/26 (0.0%) | 4/26 (15.4%) |
| | Terminal Incidence | 0/21 (0.0%) | 0/24 (0.0%) | 4/26 (15.4%) |
| | Time-to-First | ---- | ---- | 361 (T) |
| | CAFE P-Value | 0.012 * | | 0.071 |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Mammary Gland * Hyperplasia,Lobular | Simple Incidence | 10/23 (43.5%) | 13/26 (50.0%) | 23/26 (88.5%) |
| | Terminal Incidence | 10/21 (47.6%) | 13/24 (54.2%) | 23/26 (88.5%) |
| | Time-to-First | 361 (T) | 360 (T) | 360 (T) |
| | CAFE P-Value | <.001 *** | 0.433 | <.001 *** |
| | Severity Profile | 5 5 0 0 | 6 6 1 0 | 11 11 1 0 |
| | JT/SW P-Value | 0.001 ** | 0.295 | 0.002 ** |
| | RTE P-Value | 0.002 ** | 0.279 | 0.002 ** |
| Urinary System | | | | |
| Kidney * Casts Protein | Simple Incidence | 2/23 (8.7%) | 2/26 (7.7%) | 4/26 (15.4%) |
| | Terminal Incidence | 1/21 (4.8%) | 1/24 (4.2%) | 4/26 (15.4%) |
| | Time-to-First | 307 | 315 | 361 (T) |
| | CAFE P-Value | 0.297 | 0.647N | 0.395 |
| | Severity Profile | 2 0 0 0 | 1 1 0 0 | 4 0 0 0 |
| | JT/SW P-Value | 0.222 | 0.534 | 0.274 |
| | RTE P-Value | 0.232 | 0.474N | 0.232 |
| Kidney * Cyst,Cortex | Simple Incidence | 2/23 (8.7%) | 4/26 (15.4%) | 0/26 (0.0%) |
| | Terminal Incidence | 2/21 (9.5%) | 4/24 (16.7%) | 0/26 (0.0%) |
| | Time-to-First | 362 (T) | 361 (T) | ---- |
| | CAFE P-Value | 0.183N | 0.395 | 0.215N |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 0/23 (0.0%) | 5/26 (19.2%) | 4/26 (15.4%) |
| | Terminal Incidence | 0/21 (0.0%) | 3/24 (12.5%) | 4/26 (15.4%) |
| | Time-to-First | ---- | 257 | 361 (T) |
| | CAFE P-Value | 0.084 | 0.034 * | 0.071 |
| Kidney * Mineralization | Simple Incidence | 11/23 (47.8%) | 17/26 (65.4%) | 14/26 (53.8%) |
| | Terminal Incidence | 10/21 (47.6%) | 16/24 (66.7%) | 14/26 (53.8%) |
| | Time-to-First | 307 | 257 | 360 (T) |
| | CAFE P-Value | 0.407 | 0.171 | 0.447 |
| | Severity Profile | 11 0 0 0 | 10 6 1 0 | 7 5 1 1 |
| | JT/SW P-Value | 0.098 | 0.023 * ¹ | 0.064 |
| | RTE P-Value | 0.097 | 0.030 * | 0.097 |

| <i>Table 11. Nonneoplasms by Body System for Interim Sacrifice Females EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Kidney * Nephropathy | Simple Incidence | 6/23 (26.1%) | 13/26 (50.0%) | 15/26 (57.7%) |
| | Terminal Incidence | 5/21 (23.8%) | 13/24 (54.2%) | 15/26 (57.7%) |
| | Time-to-First | 56 | 360 (T) | 360 (T) |
| | CAFE P-Value | 0.020 * | 0.077 | 0.025 * |
| | Severity Profile | 4 1 0 1 | 8 5 0 0 | 10 4 1 0 |
| | JT/SW P-Value | 0.021 * | 0.051 | 0.022 * |
| | RTE P-Value | 0.020 * | 0.053 | 0.020 * |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Alimentary System | | | | |
| Liver * Clear Cell Focus | Simple Incidence | 3/22 (13.6%) | 0/26 (0.0%) | 2/26 (7.7%) |
| | Terminal Incidence | 3/18 (16.7%) | 0/22 (0.0%) | 2/23 (8.7%) |
| | Time-to-First | 361 (T) | ---- | 362 (T) |
| | CAFE P-Value | 0.331N | 0.089N | 0.419N |
| Liver * Fatty Change | Simple Incidence | 0/22 (0.0%) | 1/26 (3.8%) | 4/26 (15.4%) |
| | Terminal Incidence | 0/18 (0.0%) | 1/22 (4.5%) | 4/23 (17.4%) |
| | Time-to-First | ---- | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.028 * | 0.542 | 0.077 |
| | Severity Profile | --- | 0 0 1 0 | 0 1 3 0 |
| | JT/SW P-Value | 0.016 * | 0.179 | 0.021 * |
| | RTE P-Value | 0.019 * | 0.294 | 0.019 * |
| Liver * Hepatodiaphragmatic Nodule | Simple Incidence | 0/22 (0.0%) | 4/26 (15.4%) | 4/26 (15.4%) |
| | Terminal Incidence | 0/18 (0.0%) | 3/22 (13.6%) | 4/23 (17.4%) |
| | Time-to-First | ---- | 348 | 362 (T) |
| | CAFE P-Value | 0.077 | 0.077 | 0.077 |
| Liver * Hyperplasia,Bile Duct | Simple Incidence | 3/22 (13.6%) | 3/26 (11.5%) | 4/26 (15.4%) |
| | Terminal Incidence | 2/18 (11.1%) | 3/22 (13.6%) | 4/23 (17.4%) |
| | Time-to-First | 258 | 362 (T) | 360 (T) |
| | CAFE P-Value | 0.508 | 0.582N | 0.597 |
| | Severity Profile | 2 0 1 0 | 2 1 0 0 | 4 0 0 0 |
| | JT/SW P-Value | 0.450 | 0.593 | 0.539 |
| | RTE P-Value | 0.460 | 0.412N | 0.460 |
| Liver * Infiltration Cellular,Mononuclear Cell | Simple Incidence | 5/22 (22.7%) | 13/26 (50.0%) | 5/26 (19.2%) |
| | Terminal Incidence | 5/18 (27.8%) | 13/22 (59.1%) | 5/23 (21.7%) |
| | Time-to-First | 361 (T) | 359 (T) | 360 (T) |
| | CAFE P-Value | 0.408N | 0.049 * | 0.521N |
| | Severity Profile | 5 0 0 0 | 13 0 0 0 | 5 0 0 0 |
| | JT/SW P-Value | 0.328N | 0.973N | 0.470N |
| RTE P-Value | 0.395N | 0.024 * | 0.395N | |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Liver * Tension Lipidosis | Simple Incidence | 1/22 (4.5%) | 1/26 (3.8%) | 2/26 (7.7%) |
| | Terminal Incidence | 1/18 (5.6%) | 1/22 (4.5%) | 2/23 (8.7%) |
| | Time-to-First | 362 (T) | 362 (T) | 360 (T) |
| | CAFE P-Value | 0.434 | 0.712N | 0.564 |
| | Severity Profile | 0 1 0 0 | 0 0 1 0 | 0 1 1 0 |
| | JT/SW P-Value | 0.302 | 0.536 | 0.370 |
| | RTE P-Value | 0.313 | 0.472N | 0.313 |
| Liver * Vacuolization Cytoplasmic | Simple Incidence | 8/22 (36.4%) | 2/26 (7.7%) | 4/26 (15.4%) |
| | Terminal Incidence | 8/18 (44.4%) | 2/22 (9.1%) | 3/23 (13.0%) |
| | Time-to-First | 359 (T) | 362 (T) | 315 |
| | CAFE P-Value | 0.059N | 0.018N* | 0.090N |
| | Severity Profile | 6 2 0 0 | 1 1 0 0 | 3 1 0 0 |
| | JT/SW P-Value | 0.047N* | 0.010N** | 0.019N* |
| | RTE P-Value | 0.032N* | 0.007N** | 0.032N* |
| Pancreas * Degeneration,Acinus | Simple Incidence | 19/22 (86.4%) | 18/26 (69.2%) | 21/25 (84.0%) |
| | Terminal Incidence | 17/18 (94.4%) | 16/22 (72.7%) | 20/23 (87.0%) |
| | Time-to-First | 173 | 323 | 346 |
| | CAFE P-Value | 0.517N | 0.144N | 0.574N |
| | Severity Profile | 4 4 5 6 | 4 6 5 3 | 7 7 4 3 |
| | JT/SW P-Value | 0.119N | 0.055N | 0.086N |
| | RTE P-Value | 0.101N | 0.050N* | 0.101N |
| Pancreas * Pigmentation | Simple Incidence | 8/22 (36.4%) | 10/26 (38.5%) | 8/25 (32.0%) |
| | Terminal Incidence | 7/18 (38.9%) | 9/22 (40.9%) | 7/23 (30.4%) |
| | Time-to-First | 258 | 348 | 346 |
| | CAFE P-Value | 0.431N | 0.560 | 0.497N |
| | Severity Profile | 6 2 0 0 | 6 4 0 0 | 6 2 0 0 |
| | JT/SW P-Value | 0.373N | 0.614N | 0.454N |
| | RTE P-Value | 0.385N | 0.388 | 0.385N |
| Cardiovascular System | | | | |
| Heart * Cardiomyopathy | Simple Incidence | 16/22 (72.7%) | 24/26 (92.3%) | 23/26 (88.5%) |
| | Terminal Incidence | 14/18 (77.8%) | 21/22 (95.5%) | 21/23 (91.3%) |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Time-to-First | 258 | 323 | 315 |
| | CAFE P-Value | 0.106 | 0.077 | 0.154 |
| | Severity Profile | 11 4 1 0 | 15 7 2 0 | 14 5 4 0 |
| | JT/SW P-Value | 0.072 | 0.059 | 0.075 |
| | RTE P-Value | 0.066 | 0.062 | 0.066 |
| Endocrine System | | | | |
| Adrenal Cortex * Hyperplasia | Simple Incidence | 0/22 (0.0%) | 2/26 (7.7%) | 0/26 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 2/22 (9.1%) | 0/23 (0.0%) |
| | Time-to-First | ---- | 361 (T) | ---- |
| | CAFE P-Value | 0.629N | 0.288 | |
| | Severity Profile | --- | 0 1 1 0 | --- |
| | JT/SW P-Value | 0.444N | 0.906N | 0.583N |
| | RTE P-Value | 0.500N | 0.059 | 0.500 |
| Adrenal Cortex * Vacuolization Cytoplasmic | Simple Incidence | 0/22 (0.0%) | 3/26 (11.5%) | 3/26 (11.5%) |
| | Terminal Incidence | 0/18 (0.0%) | 2/22 (9.1%) | 3/23 (13.0%) |
| | Time-to-First | ---- | 323 | 363 (T) |
| | CAFE P-Value | 0.127 | 0.150 | 0.150 |
| | Severity Profile | --- | 0 3 0 0 | 1 2 0 0 |
| | JT/SW P-Value | 0.088 | 0.052 | 0.087 |
| | RTE P-Value | 0.074 | 0.053 | 0.074 |
| Parathyroid Gland * Hyperplasia | Simple Incidence | 7/22 (31.8%) | 6/26 (23.1%) | 4/26 (15.4%) |
| | Terminal Incidence | 7/18 (38.9%) | 5/22 (22.7%) | 4/23 (17.4%) |
| | Time-to-First | 361 (T) | 348 | 361 (T) |
| | CAFE P-Value | 0.122N | 0.361N | 0.158N |
| | Severity Profile | 3 4 0 0 | 0 6 0 0 | 1 2 1 0 |
| | JT/SW P-Value | 0.126N | 0.335N | 0.147N |
| | RTE P-Value | 0.126N | 0.311N | 0.126N |
| Pituitary Gland * Cyst,Pars Distalis | Simple Incidence | 1/22 (4.5%) | 3/26 (11.5%) | 3/26 (11.5%) |
| | Terminal Incidence | 1/18 (5.6%) | 3/22 (13.6%) | 3/23 (13.0%) |
| | Time-to-First | 361 (T) | 361 (T) | 362 (T) |
| | CAFE P-Value | 0.295 | 0.371 | 0.371 |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------------|----------------|---------------|---------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| Pituitary Gland * Hyperplasia,Pars Distalis | Simple Incidence | 4/22 (18.2%) | 7/26 (26.9%) | 2/26 (7.7%) |
| | Terminal Incidence | 4/18 (22.2%) | 6/22 (27.3%) | 2/23 (8.7%) |
| | Time-to-First | 359 (T) | 118 | 362 (T) |
| | CAFE P-Value | 0.203N | 0.357 | 0.256N |
| | Severity Profile | 3 1 0 0 | 4 2 1 0 | 1 1 0 0 |
| | JT/SW P-Value | 0.161N | 0.785N | 0.224N |
| | RTE P-Value | 0.192N | 0.190 | 0.192N |
| Thyroid Gland * Hyperplasia,C-Cell | Simple Incidence | 10/22 (45.5%) | 7/25 (28.0%) | 9/24 (37.5%) |
| | Terminal Incidence | 8/18 (44.4%) | 7/22 (31.8%) | 9/23 (39.1%) |
| | Time-to-First | 173 | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.354N | 0.174N | 0.402N |
| | Severity Profile | 3 4 3 0 | 4 2 1 0 | 4 5 0 0 |
| | JT/SW P-Value | 0.217N | 0.073N | 0.142N |
| | RTE P-Value | 0.199N | 0.065N | 0.199N |
| Thyroid Gland * Hyperplasia,Follicular Cell | Simple Incidence | 1/22 (4.5%) | 4/25 (16.0%) | 2/24 (8.3%) |
| | Terminal Incidence | 1/18 (5.6%) | 4/22 (18.2%) | 2/23 (8.7%) |
| | Time-to-First | 359 (T) | 362 (T) | 361 (T) |
| | CAFE P-Value | 0.443 | 0.216 | 0.533 |
| | Severity Profile | 0 1 0 0 | 0 0 4 0 | 0 0 2 0 |
| | JT/SW P-Value | 0.330 | 0.091 | 0.210 |
| | RTE P-Value | 0.315 | 0.072 | 0.315 |
| Thyroid Gland * Ultimobranchial Cyst | Simple Incidence | 5/22 (22.7%) | 3/25 (12.0%) | 8/24 (33.3%) |
| | Terminal Incidence | 5/18 (27.8%) | 3/22 (13.6%) | 8/23 (34.8%) |
| | Time-to-First | 353 (T) | 361 (T) | 360 (T) |
| | CAFE P-Value | 0.237 | 0.278N | 0.320 |
| Genital System | | | | |
| Epididymis * Exfoliated Germ Cell | Simple Incidence | 1/22 (4.5%) | 4/26 (15.4%) | 2/26 (7.7%) |
| | Terminal Incidence | 1/18 (5.6%) | 3/22 (13.6%) | 2/23 (8.7%) |
| | Time-to-First | 362 (T) | 348 | 362 (T) |
| | CAFE P-Value | 0.479 | 0.230 | 0.564 |
| | JT/SW P-Value | 0.396 | 0.109 | 0.243 |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | RTE P-Value | 0.359 | 0.104 | 0.359 |
| Epididymis * Hyospermia | Simple Incidence | 2/22 (9.1%) | 3/26 (11.5%) | 1/26 (3.8%) |
| | Terminal Incidence | 1/18 (5.6%) | 2/22 (9.1%) | 1/23 (4.3%) |
| | Time-to-First | 258 | 323 | 363 (T) |
| | CAFE P-Value | 0.333N | 0.581 | 0.436N |
| | Severity Profile | 0 0 1 1 | 0 0 0 3 | 0 0 0 1 |
| | JT/SW P-Value | 0.251N | 0.630N | 0.319N |
| | RTE P-Value | 0.270N | 0.362 | 0.270N |
| Epididymis * Infiltration Cellular,Lymphocyte | Simple Incidence | 0/22 (0.0%) | 1/26 (3.8%) | 3/26 (11.5%) |
| | Terminal Incidence | 0/18 (0.0%) | 1/22 (4.5%) | 3/23 (13.0%) |
| | Time-to-First | ---- | 364 (T) | 361 (T) |
| | CAFE P-Value | 0.072 | 0.542 | 0.150 |
| | Severity Profile | --- | 1 0 0 0 | 3 0 0 0 |
| | JT/SW P-Value | 0.038 * | 0.179 | 0.046 * |
| | RTE P-Value | 0.044 * | 0.279 | 0.044 * |
| Prostate, Dorsal/Lateral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 4/22 (18.2%) | 9/26 (34.6%) | 4/26 (15.4%) |
| | Terminal Incidence | 4/18 (22.2%) | 9/22 (40.9%) | 4/23 (17.4%) |
| | Time-to-First | 361 (T) | 359 (T) | 361 (T) |
| | CAFE P-Value | 0.442N | 0.171 | 0.548N |
| | Severity Profile | 4 0 0 0 | 9 0 0 0 | 4 0 0 0 |
| | JT/SW P-Value | 0.361N | 0.897N | 0.484N |
| | RTE P-Value | 0.409N | 0.101 | 0.409N |
| Prostate, Dorsal/Lateral Lobe * Inflammation,Suppurative | Simple Incidence | 18/22 (81.8%) | 25/26 (96.2%) | 25/26 (96.2%) |
| | Terminal Incidence | 17/18 (94.4%) | 22/22 (100.0%) | 22/23 (95.7%) |
| | Time-to-First | 258 | 323 | 237 |
| | CAFE P-Value | 0.069 | 0.126 | 0.126 |
| | Severity Profile | 11 7 0 0 | 13 11 0 1 | 12 13 0 0 |
| | JT/SW P-Value | 0.059 | 0.069 | 0.061 |
| | RTE P-Value | 0.051 | 0.070 | 0.051 |
| Prostate, Ventral Lobe * Infiltration Cellular,Lymphocyte | Simple Incidence | 8/22 (36.4%) | 13/26 (50.0%) | 13/26 (50.0%) |
| | Terminal Incidence | 7/18 (38.9%) | 12/22 (54.5%) | 13/23 (56.5%) |
| | Time-to-First | 173 | 118 | 361 (T) |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | CAFE P-Value | 0.222 | 0.256 | 0.256 |
| | Severity Profile | 8 0 0 | 11 2 0 0 | 12 1 0 0 |
| | JT/SW P-Value | 0.172 | 0.132 | 0.171 |
| | RTE P-Value | 0.156 | 0.132 | 0.156 |
| Prostate, Ventral Lobe * Inflammation,Suppurative | Simple Incidence | 10/22 (45.5%) | 4/26 (15.4%) | 5/26 (19.2%) |
| | Terminal Incidence | 10/18 (55.6%) | 4/22 (18.2%) | 5/23 (21.7%) |
| | Time-to-First | 353 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.034N* | 0.024N* | 0.050N |
| | Severity Profile | 9 1 0 0 | 3 1 0 0 | 5 0 0 0 |
| | JT/SW P-Value | 0.025N* | 0.015N* | 0.016N* |
| | RTE P-Value | 0.017N* | 0.010N* | 0.017N* |
| Testes * Degeneration,Seminiferous Tubule | Simple Incidence | 6/22 (27.3%) | 12/26 (46.2%) | 6/25 (24.0%) |
| | Terminal Incidence | 4/18 (22.2%) | 10/22 (45.5%) | 6/22 (27.3%) |
| | Time-to-First | 258 | 323 | 361 (T) |
| | CAFE P-Value | 0.440N | 0.148 | 0.530N |
| | Severity Profile | 3 1 0 2 | 8 1 0 3 | 6 0 0 0 |
| | JT/SW P-Value | 0.256N | 0.878N | 0.358N |
| | RTE P-Value | 0.298N | 0.101 | 0.298N |
| Hematopoietic System | | | | |
| Spleen * Hematopoietic Cell Proliferation | Simple Incidence | 0/22 (0.0%) | 2/25 (8.0%) | 0/25 (0.0%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 0/23 (0.0%) |
| | Time-to-First | ---- | 323 | ---- |
| | CAFE P-Value | 0.638N | 0.278 | |
| | Severity Profile | --- | 0 2 0 0 | --- |
| | JT/SW P-Value | 0.457N | 0.910N | 0.583N |
| | RTE P-Value | 0.500 | 0.058 | 0.500 |
| Spleen * Pigmentation | Simple Incidence | 15/22 (68.2%) | 18/25 (72.0%) | 18/25 (72.0%) |
| | Terminal Incidence | 14/18 (77.8%) | 17/22 (77.3%) | 16/23 (69.6%) |
| | Time-to-First | 173 | 348 | 315 |
| | CAFE P-Value | 0.452 | 0.512 | 0.512 |
| | Severity Profile | 6 7 1 1 | 6 11 1 0 | 7 9 1 1 |
| | JT/SW P-Value | 0.416 | 0.398 | 0.478 |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------------|----------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | <i>Treatment (ug/kg)</i> | | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | RTE P-Value | 0.413 | 0.399 | 0.413 |
| Thymus * Atrophy | Simple Incidence | 18/22 (81.8%) | 24/26 (92.3%) | 21/24 (87.5%) |
| | Terminal Incidence | 18/18 (100.0%) | 22/22 (100.0%) | 20/22 (90.9%) |
| | Time-to-First | 353 (T) | 323 | 346 |
| | CAFE P-Value | 0.370 | 0.256 | 0.449 |
| | Severity Profile | 2 1 1 14 | 0 3 5 16 | 1 2 9 9 |
| | JT/SW P-Value | 0.145N | 0.640N | 0.195N |
| | RTE P-Value | 0.160N | 0.341 | 0.160N |
| Integumentary System | | | | |
| Mammary Gland * Hyperplasia,Lobular | Simple Incidence | 2/22 (9.1%) | 3/26 (11.5%) | 2/25 (8.0%) |
| | Terminal Incidence | 2/18 (11.1%) | 2/22 (9.1%) | 2/22 (9.1%) |
| | Time-to-First | 361 (T) | 118 | 361 (T) |
| | CAFE P-Value | 0.539N | 0.581 | 0.645N |
| | Severity Profile | 0 2 0 0 | 2 1 0 0 | 2 0 0 0 |
| | JT/SW P-Value | 0.402N | 0.577N | 0.487N |
| | RTE P-Value | 0.414N | 0.416 | 0.414N |
| Nervous System | | | | |
| Brain, Cerebrum * Dilatation,Ventricle | Simple Incidence | 0/22 (0.0%) | 0/26 (0.0%) | 2/26 (7.7%) |
| | Terminal Incidence | 0/18 (0.0%) | 0/22 (0.0%) | 2/23 (8.7%) |
| | Time-to-First | ---- | ---- | 363 (T) |
| | CAFE P-Value | 0.120 | | 0.288 |
| | Severity Profile | --- | --- | 1 1 0 0 |
| | JT/SW P-Value | 0.045 * | 0.500 | 0.061 |
| | RTE P-Value | 0.061 | 0.500 | 0.061 |
| Urinary System | | | | |
| Kidney * Cyst,Cortex | Simple Incidence | 4/22 (18.2%) | 3/26 (11.5%) | 6/25 (24.0%) |
| | Terminal Incidence | 4/18 (22.2%) | 3/22 (13.6%) | 6/23 (26.1%) |
| | Time-to-First | 361 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.359 | 0.403N | 0.451 |
| Kidney * Cyst,Renal Tubule | Simple Incidence | 4/22 (18.2%) | 10/26 (38.5%) | 4/25 (16.0%) |
| | Terminal Incidence | 4/18 (22.2%) | 10/22 (45.5%) | 4/23 (17.4%) |

| <i>Table 12. Nonneoplasms by Body System for Interim Sacrifice Males EE2 Continuous Dose Arm</i> | | | | |
|--|--------------------|--------------------------|----------------|----------------|
| <i>System and Nonneoplasm</i> | | <i>Treatment (ug/kg)</i> | | |
| <i>Lesion</i> | <i>Statistic</i> | <i>Control</i> | <i>0.05</i> | <i>0.50</i> |
| | Time-to-First | 362 (T) | 361 (T) | 361 (T) |
| | CAFE P-Value | 0.467N | 0.110 | 0.573N |
| Kidney * Nephropathy | Simple Incidence | 16/22 (72.7%) | 23/26 (88.5%) | 23/25 (92.0%) |
| | Terminal Incidence | 15/18 (83.3%) | 21/22 (95.5%) | 22/23 (95.7%) |
| | Time-to-First | 173 | 346 | 346 |
| | CAFE P-Value | 0.054 | 0.154 | 0.086 |
| | Severity Profile | 9 5 2 0 | 12 7 3 1 | 13 7 2 1 |
| | JT/SW P-Value | 0.122 | 0.108 | 0.128 |
| | RTE P-Value | 0.112 | 0.106 | 0.112 |

P-values for dose trend are presented in the "Control" column.

N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.

¹ Nonsignificant SW test due to the assumption of monotonicity.