

**Memorandum**

Date July 24, 2007

From Mary E. Shackelford, Ph.D.
Toxicology Group II , Division of Food Contact Notifications (DFCN)

Subject Review of Two-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in the Feed to CD-1® Swiss Mice, RTI Identification Number 65C-09301.000.003/0209301 000.003 ; Submitted to FMF 000580, Volumes I-VIII

To Michelle Twaroski, Ph.D.
Team Leader, Toxicology Group 1, DFCN

AD

**INTRODUCTION****A. Study Design**

A two generation (one litter per generation) reproductive toxicity study was conducted in CD-1® Swiss mice by administering bisphenol A in the diet at low doses to known toxic doses. ¹ The dietary bisphenol A (BPA) was administered to nine groups of 6 week old mice at dose levels of 0 (2 groups), 0.018, 0.18, 1.8, 30, 300, or 3500 ppm BPA. This resulted in estimated BPA intakes of ~ 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg/day, respectively. A positive control group was administered 17β-estradiol (E2) at a dietary concentration of 0.5 ppm which resulted in an E2 dietary intake of ~0.08 mg/kg/day. ²

The F0 generation (28/sex/group) were exposed for eight weeks before mating, during the two week mating period, the ~ 20-day gestation period, and a three week lactation period. The F1 offspring were selected at weaning so that there were 28 offspring/sex/group and the F0 dams were necropsied. The F1 offspring were similarly exposed through pre-mating, mating, gestation, and lactation. The F1 dams and the F2 offspring were necropsied at the time of weaning of the F2 offspring. The F0 and F1 males were necropsied at the end of the gestation of the F1 and F2 litters, respectively.

The study design also provided for the retained males. These were the F1 males who were selected one/litter from each dose group. These males were exposed to the respective BPA dietary treatment groups for three months and were then necropsied.

B. Study Objectives

There were four study objectives

1) Bisphenol A was administered in the feed to CD-1® Swiss mice at concentrations and doses from low to known toxic levels to evaluate the potential of BPA to produce parental and/or offspring systemic toxicity.

2) Bisphenol A was administered in the feed to CD-1® Swiss mice at concentrations and doses from low to known toxic levels to evaluate the potential of BPA to produce alterations in parental fertility, maternal pregnancy, and growth and development of the offspring for two generations.

3) The positive control of dietary estradiol was included to confirm the sensitivity of the mouse model to a potent endogenous estrogen

4) The study included two vehicle control groups to define the intrinsic variability of the endpoints of interest and to increase the historical database in mice.

C. Guidelines

This study was performed in compliance with OECD Principles of Good Laboratory Practice (GLP, OECD, 1998 and 2002). The study was designed and conducted according to the OECD Test Guideline Number 416 (OECD, 2001) which is referred to as "Two-generation Reproductive Toxicity Study."

D. Testing Facility and Sponsor

Test Facility: RTI International
Center for Life Sciences and Toxicology
P.O. Box 12194, 3040 Cornwallis Road
Research Triangle Park, NC 27709-2194

Sponsor: American Plastics Council
1300 Wilson Boulevard
Arlington, VA 22209

E. Study Dates

Initiation Date: March 14, 2005
Experimental Start Date: March 21, 2005
Completion Date: October 27, 2006
Audit of Draft Final Report: October 30, 2006
Final Report Date: March 1, 2007

F. Test Substances

Bisphenol A: The BPA (Cas No. 80-05-7) was obtained from Fisher Scientific (Pittsburgh, PA, from Acros Organics, NV, Fairlawn, NJ) The test substance was an opaque, white, granular solid. It was identified as Supplier Lot No B00701-38.

Estradiol: The estradiol (Cas No. 50-28-2) was provided by Sigma-Aldrich (St. Louis, MO) It was identified as Supplier Batch # 021K1267.

Purity BPA: The BPA was 99.76% pure on November 5, 2004 and 99.70% pure on November 3, 2005.

Purity E2: The E2 was 99.0% pure on March 7, 2005 and 98.94% pure on February 13, 2006

G. Parameters Measured in Parents and Offspring

The following parameters were measured in the F0 and F1 male and female parental animals:

1. Body weights, food consumption, clinical observations
2. F0 and F1 males were necropsied at the end of the gestation of their F1 and F2 litters, respectively. Andrologic and histopathologic assessments were performed. Male andrology was measured by the following in adult F0 and F1 males and F1 retained males: percent motile sperm, percent progressively motile sperm, epididymal sperm concentration, spermatid head concentration, daily sperm production per testis, efficiency of daily sperm production, and percent abnormal sperm.
3. F0 and F1 females were examined for estrous cyclicity by daily vaginal smears for the last three weeks of their pre-mating exposure. At weaning of the F1 and F2 litters, respectively, the F0 and F1 females were examined for stage of estrous, organ weights, ovarian primordial follicle counts, and histopathology.
4. All adult necropsies included body weights, gross examination of all cavities and organs, weights of selected organs, and histopathology of selected organs for F0 and F1 adults. The selected organs weighed included: brain, pituitary, thyroid, liver, spleen, kidney, adrenal, and reproductive organs. The selected histopathology included: adrenal, kidney, liver, spleen, thyroid, pituitary, and reproductive organs.
5. Mating, fertility, and gestational indices were calculated.
6. The retained F1 males consisted of one F1 male/litter randomly selected at weaning to be retained for three months with exposure continuing, with necropsy, andrology, and histopathology concurrent with the F1 parental males

The following parameters were measured in the F1 and F2 offspring on the specified postnatal days (PND):

1. All live pups were counted, sexed, and examined as soon as possible on the day of birth (designated PND 0) to determine the number of viable and stillborn pups in each litter.
2. Dead pups were counted, sexed, and examined externally and visceraally, if possible.
3. All live F1 and F2 pups were individually counted, sexed, weighed, and examined grossly on PND 0, 4, 7, 14, and 21. The body weights and sexes were recorded on an individual basis, but the pups were not uniquely identified at this stage.
4. The F1 and F2 offspring were evaluated for anogenital distance (AGD) at birth and on PND 21.
5. On PND 4, the size of the F1 and F2 litters was culled to 10 pups, with 5 males and 5 females, if possible. All culled pups were sacrificed by decapitation and examined for visceral alterations, especially those of the reproductive system.
6. Starting on PND 18, each F1 female pup selected to produce the F2 litters was observed for vaginal patency. Observations were continued until every female selected had this response. The date, age, and body weight were recorded for each female on the day of acquisition.
7. During the pre-mating exposure period, each F1 male was observed for cleavage of the balanopreputial gland (PPS), beginning on PND 22. The date, age, and body weight were recorded for each male on the day of acquisition. Each male's body weight on PND 30 was recorded.
8. All weanling necropsies included body weights, gross examination of all cavities and organs, weights of selected organs (brain, thymus, spleen, liver, kidney, reproductive organs) and histopathology of selected organs (brain, liver, kidney, spleen, thymus, and reproductive organs) for F1 and F2 weanlings.

II. RESULTS

In the following review memo, the reviewer has included tables of numerical data where the high dose (3500 ppm) of bisphenol A showed a similar response in the reproductive or offspring parameters to the 0.5 ppm 17 β -Estradiol positive group. In addition, in parentheses there are citations of tables which contain summary data. These tables refer to the Summary Tables which are located in Volume II of VIII of the Final Report for this two generation reproduction study in mice. A list of these summary tables is located in Attachment 1. A copy of this two generation reproduction study in mice is located in FMF 000580.

A. Parental systemic parameters measured in F0 and F1 males (including retained F1 males) and females with no treatment related findings at any dose level of BPA

1. Feed consumption in g/day and g/kg/day was variable and showed no clear treatment-related effects in either sex. Feed efficiency showed no treatment related changes (Tables 4, 9, 13, 16, 29, 35, 39, 42, 55).

2. Measurements of body weight and body weight change were variable and showed no clear treatment-related effects in either sex (Tables 3, 8, 12, 15, 28, 38, 41, 54).

2. There were no treatment- or dose- related clinical observations in either sex in any of the generations (Tables 5, 10, 14, 17, 30, 36, 40, 43, 56).

3. At necropsy of the adults, F0, F1, and F1 retained males showed no treatment-related effects on the following absolute or relative organ weights: brain, pituitary, thyroid, spleen, and adrenal (Tables 6 and 31 and 57).

4. At necropsy of the adults, F0 and F1 females showed no treatment-related effects on the following absolute or relative organ weights: brain, pituitary, thyroid, spleen, and adrenal (Table 24 and 50).

5. There were no treatment- or dose-related gross or microscopic findings for the following examined organs for F0, F1, or F1 retained males: pituitary, spleen, adrenal, and thyroid (Table 7 and 32 and 58).

6. There were no treatment- or dose-related gross or microscopic findings for the following examined organs for F0 and F1 females: pituitary, spleen, adrenal, mammary, and thyroid (Table 25 and 51).

B. Parental Reproductive Parameters measured in the F0 and F1 males and females with no treatment-related findings at any dose level of BPA

1. There were no treatment-related findings on F0 or F1 female estrous cyclicity, number of ovarian primordial follicle counts/female, weights of the paired ovaries, or weights of the uterus plus cervix plus vagina at any dose of BPA (Tables 11, 24, 37, and 50).

2. In the F0 or F1 males (including retained males), there were no treatment related effects on andrology assessments: percent motile sperm, percent progressively motile sperm, spermatid head concentration, daily sperm concentration, daily sperm production per testis, efficiency of daily sperm production, and percent abnormal sperm. In the F0 or F1 males (including

retained males), there were no treatment related effects on the weight of the paired testes, seminal vesicles plus coagulating glands, and prostate weight (ventral lobe, dorsolateral lobe, or total prostate) (Tables 6, 31, and 57).

3 Mating, fertility, or gestational indices were not affected in the F0 or F1 parents (Table 18 and 44).

4. The microscopic analysis reported an increased incidence of uni-/bilateral paraovarian cysts in the F0 and F1 parental females in the 3500 BPA dose level (Tables 25 and 51). In the final report (page 118, Volume 1 of VIII), the study authors provided a reasonable rationale to explain why this finding is not attributable to BPA.

5. In the F0 or F1 reproductive indices, there were no treatment-related effects on the number of pups/litter, sex ratio, percent post-implantation loss, or the indices for stillbirth, live birth or offspring survival (Tables 18, 19, 44 and 45).

C. Parameters measured for the offspring (F1 and F2) with no treatment-related findings at any dose level of BPA

1. There were no effects on the F2 pup body weights from PND 0 to PND 21 at any BPA dose level (Table 45). However the F1 pup body weights were significantly decreased from PND 7 to 21 at the 3500 ppm BPA dose level (Table 19)

2. At necropsy of the F1 and F2 male and female weanlings on PND 21, there were no treatment-related effects on the following absolute or relative organ weights: brain, thymus, liver, or kidney (Tables 22 and 48).

3. At necropsy of the F1 and F2 male weanlings on PND 21, there were no treatment-related effects on the following absolute or relative organ weights: paired epididymis weight and seminal vesicles with coagulating glands (Tables 22 and 48).

4. At necropsy of the F1 and F2 female weanlings on PND 21, there were no treatment-related effects on the following absolute or relative organ weights: paired ovary weight and uterus with cervix and vagina (Table 22 and 48)

5. At necropsy of the F1 and F2 male/female weanlings on PND 21, there were no treatment-related effects on the histopathology of the following organs: brain, kidney, liver, and spleen (Tables 23 and 49). The microscopic analysis reported an increased incidence of centrilobular hepatocyte cytoplasmic alteration at the 3500 ppm and 300 ppm BPA dose levels in the F1/F2 male and female weanlings. In the final report (page 118-119, Volume 1 of VIII), the study authors provided a reasonable rationale to explain why these findings are not attributable to BPA.

6. At necropsy of the F1 and F2 male weanlings on PND 21, there were no treatment-related effects on the histopathology of the following organs: epididymis or seminal vesicle (Tables 23 and 49)

7. At necropsy of the F1 and F2 female weanlings on PND 21, there were no treatment-related effects on the histopathology of the following organs: cervix, ovary, vagina, and

uterine horn (Tables 23 and 49) There was an increased incidence of vaginal epithelial keratinization in F2 weanling females at the 3500 ppm BPA group. In the final report (page 119, Volume 1 of VIII), the study authors provided a reasonable rationale to explain why this finding is not attributable to BPA.

8. At birth (PND 0) of the F1 and F2 male/female offspring, there were no effects on the average or average adjusted male/female pup anogenital distance per litter (Tables 19 and 45)

9. At necropsy of the F1 and F2 female offspring on PND 21, there were no effects on the anogenital distance and the adjusted anogenital distance (Tables 22 and 48).

10. At necropsy of the F2 male offspring on PND 21, there were no effects on the anogenital distance and the adjusted anogenital distance (Table 48). At necropsy of the F1 male offspring on PND 21 (Table 22), there was a decreased anogenital distance and adjusted anogenital distance. In the final report (page 71, Volume 1 of VIII), the study authors provided a reasonable rationale to explain why this finding is not attributable to BPA.

11. There were no treatment related effects on acquisition of puberty as measured for the F1 female offspring (Table 33). This parameter was not measured in the F2 female offspring.

D. Parental systemic parameters measured F0 and F1 males (including F1 retained males) and females with treatment-related findings at the 3500 ppm BPA dose level (estimated intake of 600 mg/kg/day of BPA)

1. At necropsy of the F0 and F1 adult male and female animals, there were statistically significant increased liver weights, relative liver weights (percent body weight), and relative liver weights (percent brain weight) (Tables 6, 24, 31 and 50).

2. At necropsy of the F0 and F1 adult male and female animals, there was an increased incidence of minimal to mild centrilobular hepatocyte hypertrophy (Tables 7, 25, 32, and 51).

3. At necropsy of the F0 and F1 adult male and female animals, there were statistically significant increased kidney weights, relative kidney weights (percent body weight), and relative kidney weights (percent brain weight) (Tables 6, 24, 31, and 50).

4. At necropsy of the F0 and F1 adult male and female animals, there was an increased incidence of minimal to mild nephropathy (Tables 7, 25, 32, and 51).

5. At necropsy of the F1 adult retained males, the following were observed: statistically significant increased kidney weights, statistically significant increased relative kidney weights, significantly increased relative liver weights, increased incidence of minimal to mild centrilobular hepatocyte hypertrophy, and increased incidence of minimal to mild nephropathy (Tables 57 and 58).

E. Parental reproductive parameters measured in F0 and F1 males and females with treatment-related findings at the 3500 ppm BPA dose level (estimated intake of 600 mg/kg/day of BPA)

1. At necropsy of the F0 males at the 3500 ppm dose level, the epididymal sperm concentration was significantly reduced (Table 6) At necropsy of the F0 males at the 3500

ppm dose level, the paired epididymal weights (absolute, relative to body weight, relative to brain weight) were reduced but did not achieve statistical significance (Table 6). At necropsy of the F0 males at the 3500 ppm dose level, the macroscopic findings included 2 out of 10 males with epididymus (right) reduced in size but none of the 55 control males had this finding (Table 7). In the F1 males and the F1 retained males at the 3500 ppm dose level, there were no statistically significant effects on these parameters with the exception of the significantly reduced absolute paired epididymal weights in F1 males (Tables 31 and 57).

2. The gestational length (days) was statistically significantly increased for both the F0 and the F1 generations at 3500 ppm (Tables 18 and 44).

Gestation Length in Days as Measured in the F0 and F1 females

Bisphenol A (ppm in feed)								17β-Estradiol (ppm feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
F0	19.0	19.0	18.9	19.1	18.9	19.1	19.3*	19.6*
F1	19.0	18.9	18.9	19.1	19.0	19.0	19.3*	19.4*

* Statistically significant, $p < 0.05$, Individual t-test for pairwise comparisons to control for robust regression model

F. Parameters measured in offspring (F1 and F2) with treatment related findings at the 3500 ppm BPA dose level (estimated intake of 600 mg/kg/day of BPA)

1. The F1 pup body weights were significantly decreased from PND 7 to 21 at the 3500 ppm BPA dose level (Table 19).

2. At necropsy of the F1 and F2 male and female weanlings, there were statistically significant reductions in absolute and relative spleen weights (Tables 22 and 48).

3. At necropsy of the F1 and F2 male weanlings, the macroscopic observations showed an increased incidence of pups with undescended testes (Table 23 and 49). There was no statistical analysis in the report for this parameter.

Measurements of Undescended Testes in F1 and F2 Pups as reported in Tables 23 and 49

Bisphenol A (ppm in the feed)								17β-Estradiol (ppm in the feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
F1 pup	8/135 5%	2/79 2.5%	3/54 5.6%	8/70 11.4%	4/78 5.1%	4/68 5.9%	9/56 16.7%	24/53 45.3%
F2 pup	8/249 3.2%	1/120 0.8%	7/120 5.8%	6/124 4.8%	1/118 0.8%	10/100 10%	14/96 14.6%	36/76 47%

4. There was an increased incidence and severity of seminiferous tubule hypoplasia in the testes of F1 and F2 weanling males at 3500 ppm which is consistent with the decreased testes weights in these groups (Tables 22, 23, 48, and 49). The report did not provided statistical analysis of the histopathology findings.

Measurements of seminiferous tubule hypoplasia in the testes of F1 and F2 Weanling Pups as reported in Tables 23 and 49

	Bisphenol A (ppm in the feed)							17 β - Estradiol (ppm in the feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
F1 pup	1/96 1.0%	0/54 0%	0/37 0%	1/45 2.2%	3/51 5.8%	2/45 4.4%	5/43 11.6%	10/43 23.3%
F2 pup	5/114 4.4%	1/53 1.9%	2/61 3.3%	2/55 3.6%	0/51 0%	5/49 10.2%	20/57 35.1%	17/66 25.8%

Measurements of Absolute Paired Testes Weights (gm) in F1 and F2 Weanling Pups as reported in Table 22 and 48

	Bisphenol A (ppm in the feed)							17 β - Estradiol (ppm in the feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
F1 pup	0.0534	0.0547	0.0546	0.0561	0.0559	0.0570	0.0426 ^c	0.0394 ^c
F2 pup	0.0594	0.0573	0.0591	0.0571	0.0612	0.0598	0.0525 ^a	0.0427 ^c

^a Statistically significant, p < 0.05, Individual t-test for pairwise comparison to control for correlated data

^b Statistically significant, p < 0.01, Individual t-test for pairwise comparison to control for correlated data

^c Statistically significant, p < 0.001, Individual t-test for pairwise comparison to control for correlated data

5. One developmental effect related to BPA in the F1 male offspring was the delayed acquisition of the preputial separation in the 3500 ppm BPA group (Table 27 and 53)

Measurement of Day of Male Preputial Separation in F1 Weanling Pups and F1 Retained Males as reported in Table 27 and 53

	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0	0.018	0.18	1.8	30	300	3500	0.5
F1 pup								
Absolute	26.0	26.0	26.1	25.9	25.9	26.3	27.9 ^{aa}	32.8 ^{aaa}
Adjusted	26.2	26.1	26.2	26.0	26.3	26.3	28.2 ^{bbb}	31.6 ^{bbb}
Retained F1 males								
Absolute	26.6	26.3	26.3	25.9	25.9	26.5	28.3 ^{aa}	33.3 ^{aaa}
Adjusted	26.6	26.2	26.5	26.0*	26.0	26.5	28.4 ^{bb}	32.6 ^{bbb}

Absolute = the value on the day of preputial separation

Adjusted = adjusted to the body weight on the day of preputial separation

^{aa} Statistically significant, $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model for absolute values

^{aaa} Statistically significant, $p < 0.001$, Individual t-test for pairwise comparisons to control in robust regression model for absolute values

^{bb} Statistically significant, $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition as covariate

^{bbb} Statistically significant, $p < 0.001$, Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition as covariate

G. Parameters measured with treatment related findings at the 300 ppm BPA dose level (estimated intake of 50 mg/kg/day of BPA)

1. One treatment-related effect observed was an increased incidence of centrilobular hepatocyte hypertrophy of minimal to mild severity in adult F0 males, retained F1 males, and F1 females (Tables 7, 25, 32, 51 and 58).

2. The increased kidney weights in the F0 males (300 ppm) and F1 males (1.8, 30 and 300 ppm) were not considered to be treatment-related. In the report (Volume 1 of VIII, pages 70 and 72), the study authors provided a reasonable rationale to explain why these findings are not attributed to treatment with BPA.

H. Parameters measured with no treatment-related findings at the 300 ppm BPA dose level (estimated intake of 50 mg/kg/day of BPA)

1. There were no treatment-related findings on the parental reproductive or offspring parameters at 300 ppm BPA.

I. Absence of treatment related findings at low doses of BPA from 30, 1.8, 0.18, 0.018 ppm (estimated intake of 5, 0.3, 0.03, 0.003 mg/kg/day of BPA)

1. At 0.018, 0.18, 1.8, or 30 ppm BPA (estimated intakes of 0.003, 0.03, 0.3, or 5 mg/kg/day of BPA), this study did not identify treatment-related systemic, developmental, or reproductive effects.

J. Treatment related findings in the 0.5 ppm 17 β -Estradiol Positive Group (E2 intake of ~0.08 mg/kg/day)

At this dose level of the positive control, the reproductive toxicity was expressed as the following and are consistent with Tyl et al. 2006².

1. Reduced fertility index in F1 females (Tables 18 and 44)
2. Increased stillbirth index in F0 and F1 females (Tables 18 and 44)
3. Reduced livebirth index in F0 and F1 females (Tables 18 and 44)
4. Reduced litter sizes in F0 and F1 females (Tables 18 and 44)
5. Gestational length was increased in F0 and F1 females (Tables 18 and 44)
6. Reduced anogenital distance in F1/F2 males on PND 21 (but not on PND 0) (Tables 19, 22, 45 and 48)
7. Delay in preputial separation in F1 males (parameter not measured in F2)(Table 27)
8. Decreased testes and epididymal weights in the F1/F2 male weanlings (Tables 22 and 48)
9. F1 and F2 weanling males exhibited increased incidences of seminiferous tubule hypoplasia of the testis and of undescended testes (Tables 23 and 48)
10. Acceleration of puberty in F1 females (parameter not measured in F2) (Table 33)
11. Increased weights of the uterus plus cervix plus vagina in F0/F1 adults and F1/F2 weanlings (Tables 22, 24, 48 and 50)
12. The F1 and F2 weanling females exhibited increased incidences (>90%) of vaginal epithelial keratinization and bilateral luminal dilatation of the uterine horns (Tables 23 and 49).

III. CONCLUSIONS

In summary, the study reported adult systemic toxicity and reproductive and offspring toxicity. At 3500 ppm in the F0 and F1 males and females, adult systemic toxicity included. 1) increased liver and kidney weights, 2) an increased incidence of minimal to mild nephropathy, and 3) an increased incidence of minimal to mild centrilobular hepatocyte hypertrophy. Systemic toxicity in the male (F0 and retained F1) and female (F1) adults at the 300 ppm dose level was limited to an increased incidence of minimal to mild centrilobular hepatocyte hypertrophy. Reproductive and offspring toxicity were reported at the 3500 ppm dose level and included: 1) increased gestation length in F0 and F1 females, 2) decreased epididymal sperm concentration and weights in the F0 males, 3) increased incidence of hypoplasia of the seminiferous tubules in F1/F2 male weanlings, 4) increased incidence of undescended testes in F1/F2 male weanlings, 5) reduced testes weights in F1/F2 male weanlings, and 6) reduced spleen weights in F1/F2 male and female weanlings

1. The NOEL for systemic toxicity is 30 ppm BPA (estimated intake of 5 mg/kg/day).
2. The NOEL for reproductive toxicity and offspring toxicity is 300 ppm BPA (estimated intake of 50 mg/kg/day).
3. In this study the estradiol like effects attributed to BPA were at the 3500 ppm BPA dose level (~ 600 mg/kg/day of BPA) and were observed in the male offspring.
 - a. In the F1/F2 male weanlings the following were observed at weaning sacrifice: an increased incidence of hypoplasia of the seminiferous tubules, increased incidence of undescended testes, and statistically significantly reduced testes weights.
 - b. One developmental effect related to BPA in the F1 male offspring was the delayed acquisition of the preputial separation in the 3500 ppm BPA group.

IV. COMMENTS

1. There was no statistical analysis of the macroscopic and microscopic data in Tables 7, 23, 25, 32, 49, 51, and 58 of the report. In response to an FDA inquiry on May 15, 2007 to the American Plastics Council, the attached response was sent from Dr. Rochelle Tyl of RTI International to Dr. Steven Hentges of the American Plastics Council (dated June 6, 2007). A copy of the response is located in Attachment 2. This response is adequate.
2. The safety assessment of bisphenol A could be further refined with a study of the reproductive and developmental effects of bisphenol A in a nonrodent animal model for two reasons: 1) differences in comparative embryology of the rodent and nonrodent³ and 2) dose of bisphenol A to the postnatal rodent cannot be measured.⁴

V. CITED REFERENCES

- ¹ Two Generation Reproductive Toxicity Evaluation of Bisphenol A (BPA; Cas No. 80-05-7) Administered in the Feed to CD-1 ® Swiss Mice (Modified OECD 416), Study Authors: R.W. Tyl, PhD, DABT, C.B. Myers, MS, and M.C. Marr, BA, RLATG. Test Facility: RTI International, RTP, NC, Sponsor: American Plastic Council, Virginia, Final Report Date: March 1, 2007.
- ² Two Generation Reproductive Toxicity Evaluation of 17 Estradiol (E2, Cas No. 50-28-2) Administered in the Feed to CD-1 ® Swiss Mice (Modified OECD 416), Study Authors: R. W. Tyl, PhD, DABT, C. B. Myers, M.S., and M C. Marr, BA, RLATG. Test Facility: RTI International, RTP, NC, Sponsor: American Plastics Council, Virginia, Final Report Date: July 11, 2006.
- ³ DeSesso, JM, Comparative Embryology. (1997) In: Handbook of Developmental Toxicology, edited by Ronald D. Hood, CRC Press, pages 111-174.
- ⁴ Tyl, RW et al. Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats (2003) Toxicological Sciences, volume 68, 121-146.



Mary F. Shackelford, PhD (HFS-275)
Toxicology Group II, DFCN/OFAS/CFSAN

ATTACHMENTS:

1. Section VI. Summary Tables in Volume II of VIII of Final Report, Table of Contents
2. Response from Dr Rochelle W. Tyl, PhD of RTI International to Dr. Steve Hentges of the American Plastics Council, June 6, 2007.

Attachment 1

VI. SUMMARY TABLES IN VOLUME II of VIII OF FINAL REPORT (FMF 580)

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Attachment 1

VI. SUMMARY TABLES IN VOLUME II of VIII OF FINAL REPORT(FMF 580)

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Attachment 2



Life Sciences and Toxicology Research, Health Sciences

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June 6, 2007

Dr. Steven G. Hentges
American Chemistry Council
1300 Wilson Blvd
Arlington, VA 22209

Dear Steve:

It is my understanding that the FDA contacted you during their review of the recently completed "Two Generation Reproductive Toxicity Evaluation of Bisphenol A (BPA, CAS No. 80-05-7) Administered in the Feed to CD-1® Swiss Mice (Modified OECD 416)," asking that we provide a supplement to the record containing a statistical analysis of the histopathology data from this study. These analyses do not exist for this study and cannot be readily generated.

Statistical analyses of findings are not a routine part of histopathologic evaluations in reproductive toxicology studies (or for that matter in most studies, except for tumor incidence in carcinogenesis/chronic studies). There are a number of reasons why statistics are not conducted. They include: the methods employed often do not allow statistics (e.g., not all animals are examined), frequently grades of lesions are used (and may be important), leading to very complicated statistical analyses that ultimately provide nothing additional to the pathologist's conclusions, and rare lesions may be treatment related (i.e., biologically significant) but not statistically significant.

In the two-generation study with BPA, there were several histopathological findings that required interpretation to arrive at appropriate conclusions regarding relationship to treatment. In none of these cases was it possible, helpful and/or necessary to conduct statistical analyses to reach these conclusions. A review of these findings in regard to statistical analyses follows (these lesions are also reviewed in detail in the Discussion section of the report):

1 Increased incidence and severity of centrilobular hepatocellular hypertrophy

BPA has been extensively studied in rodent species (rats and mice), including in the range-finding (13 weeks) study for the two-generation study. Centrilobular hepatocellular hypertrophy is a consistent lesion in these studies at high BPA doses. Evaluation of the relationship to treatment in the two-generation study relies on this background information, as well as differences in severity of the lesion; therefore, statistical evaluation provides no useful support.

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2. Slight increased incidence of nephropathy of unknown toxicological significance in the kidneys

Similar to the lesions in the liver, BPA tends to minimally affect the kidney in many studies (also at high doses). In this case, the lesion is so minor as to be difficult to conclude toxicological relevance. Statistical analyses would not change this conclusion.

3. An increased incidence of paraovarian cysts in the ovaries of adult F0 and F1 females exposed to 3500 ppm BPA and 0.5 ppm E2

The pathogenesis of this lesion and the high spontaneous incidence in mice identified in the literature led to the conclusion that the differences were not attributable to E2 or BPA. The evaluation of multiple sections in the high-dose groups, not done for the lower dose groups, precludes the use of statistical analyses, even if such statistics would be of use. However, the incidence is clearly increased in this lesion and, thus, statistical analyses would provide no additional useful information.

4. Centrilobular hepatocellular cytoplasmic alteration in the liver in weanling animals

For this finding, considerable scientific interpretation was required to establish the conclusion that "Based on the background incidence in controls, the inconsistency of findings across generations, the limited severity of the alteration, the uncertain etiology, and the lack of related toxicologic effects, this alteration in morphology of the liver was not considered to be toxicologically significant in the weanling animals." There is also no historical (or published) control data for histopathologic evaluations of weanling organs. Statistical analyses would not provide any additional information useful to this extensive evaluation of the effect.

5. An increased incidence and severity of seminiferous tubule hypoplasia in the testes

This finding correlated with testes weight reductions and was considered by the pathologist to be related to a delay in testicular development (also associated with delayed testis descent and preputial separation, all consistent with delay). Statistical analyses would not change this conclusion.

6. An increased incidence (>90%) of vaginal epithelial keratinization and an increased incidence (>95%) of luminal dilatation of the uterine horns (bilateral) at 0.5 ppm E2

These lesions were clearly related to treatment with the positive control, E2, and statistical analyses would add no useful information.

Lastly, the BPA two-generation study was commissioned in response to a request by the European Union for a risk assessment of BPA. As part of this process, the EU formed a Scientific Steering Committee consisting of reproductive and developmental toxicity experts from several Member States including UK, Germany, Netherlands and others. The committee had extensive oversight and input into the design of all phases of the

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project (including both the E2 and BPA studies) and reviewed all draft reports in great detail. Comments from the committee have been incorporated into the final reports. To my knowledge, statistical analyses of the histopathology findings for the referenced study have not been requested by these reviewers, indicating general agreement that such analyses are not needed to reach appropriate conclusions. The study has been accepted for use in completing the European Union Risk Assessment.

Please do not hesitate to request any further information that you may need for your evaluation of this study.

Sincerely,

/s/
/s/

Rochelle W. Tyl, Ph.D., DABT
Study Director and
Senior Fellow, Developmental and
Reproductive Toxicology (DART)
Director, DART Studies

Table 6. Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 1 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. of F ₀ Males at Scheduled Sacrifice	56	28	28	28	28	28	28	28
Sacrifice Body Weight (g) ^b	39.53 ± 0.50 N=56	40.05 ± 0.64 N=28	39.35 ± 1.05 N=28	40.34 ± 0.61 N=28	40.26 ± 0.67 N=28	39.47 ± 0.53 N=28	40.08 ± 0.79 N=27 ^c	38.65 ± 0.50 N=28
Brain Weight (g) ^b	0.5175 ± 0.0041 N=55 ^d	0.5188 ± 0.0048 N=28	0.5172 ± 0.0062 N=28	0.5184 ± 0.0049 N=28	0.5123 ± 0.0064 N=28	0.5143 ± 0.0078 N=28	0.5335 ± 0.0060 N=28	0.5248 ± 0.0073 N=28
Pituitary Weight (g) ^b	0.0027 †† ± 0.0001 N=54 ^e	0.0027 ± 0.0001 N=28	0.0027 ± 0.0001 N=27 ^e	0.0027 ± 0.0001 N=28	0.0027 ± 0.0001 N=26 ^e	0.0028 ± 0.0001 N=26 ^e	0.0029 ± 0.0001 N=28	0.0031 †† ± 0.0001 N=28
Thyroid Weight (g) ^b	0.0030 ± 0.0001 N=56	0.0029 ± 0.0001 N=27 ^e	0.0030 ± 0.0001 N=26 ^e	0.0030 ± 0.0001 N=27 ^e	0.0032 ± 0.0001 N=27 ^e	0.0031 ± 0.0001 N=27 ^e	0.0032 ± 0.0001 N=27 ^e	0.0029 ± 0.0001 N=25 ^e
Liver Weight (g) ^b	2.1349 ††† ± 0.0295 N=56	2.1600 ± 0.0482 N=28	2.1754 ± 0.0552 N=28	2.2160 ± 0.0415 N=28	2.2398 ± 0.0415 N=28	2.2104 ± 0.0478 N=28	2.5217 ††† ± 0.0563 N=28	2.2252 ± 0.0321 N=28
Spleen Weight (g) ^b	0.1162 ± 0.0038 N=55 ^f	0.1184 ± 0.0068 N=28	0.1208 ± 0.0080 N=28	0.1113 ± 0.0059 N=28	0.1192 ± 0.0059 N=28	0.1157 ± 0.0046 N=28	0.1165 ± 0.0055 N=28	0.1108 ± 0.0045 N=28
Right Kidney Weight (g) ^b	0.3926 ††† ± 0.0059 N=56	0.3924 ± 0.0098 N=28	0.3931 ± 0.0093 N=28	0.4019 ± 0.0077 N=28	0.4114 ± 0.0121 N=28	0.4220 ± 0.0082 N=28	0.4753 ††† ± 0.0127 N=28	0.4210 ± 0.0104 N=28

Table 6 Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 2 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Left Kidney Weight (g) ^b								
#	0.3802 †††	0.3796	0.3744	0.3878	0.4037	0.4139 †††	0.4587 †††	0.4030 †
	± 0.0055	± 0.0103	± 0.0086	± 0.0080	± 0.0137	± 0.0085	± 0.0110	± 0.0088
	N=56	N=28	N=28	N=28	N=28	N=28	N=28	N=28
Paired Adrenal Gland Weight (g) ^b								
	0.0074	0.0064	0.0061	0.0072	0.0068	0.0069	0.0070	0.0067
	± 0.0004	± 0.0004	± 0.0004	± 0.0007	± 0.0005	± 0.0004	± 0.0004	± 0.0005
	N=54 ^g	N=27 ^f	N=28	N=28	N=27 ^g	N=28	N=28	N=28
Paired Testis Weight (g) ^b								
	0.2601	0.2592	0.2715	0.2616	0.2483	0.2654	0.2508	0.2644
	± 0.0041	± 0.0054	± 0.0064	± 0.0063	± 0.0079	± 0.0076	± 0.0085	± 0.0061
	N=55 ^h	N=28	N=28	N=28	N=28	N=28	N=28	N=28
Paired Epididymis Weight (g) ^b								
	0.1147	0.1167	0.1135	0.1183	0.1143	0.1143	0.1134	0.1146
	± 0.0015	± 0.0024	± 0.0023	± 0.0029	± 0.0023	± 0.0025	± 0.0031	± 0.0025
	N=56	N=26 ^{f,i}	N=28	N=27 ⁱ	N=28	N=28	N=28	N=28
Seminal Vesicles with Coagulating Gland Weight (g) ^b								
	0.3861	0.4014	0.3892	0.4202	0.4054	0.3963	0.4030	0.3933
	± 0.0117	± 0.0176	± 0.0176	± 0.0197	± 0.0171	± 0.0179	± 0.0207	± 0.0176
	N=56	N=28	N=28	N=28	N=27 ^j	N=28	N=28	N=28
Ventral Prostate Weight (g) ^b								
	0.0348	0.0381	0.0374	0.0260	0.0321	0.0327	0.0304	0.0386
	± 0.0026	± 0.0037	± 0.0025	± 0.0028	± 0.0024	± 0.0029	± 0.0027	± 0.0040
	N=56	N=28	N=28	N=28	N=27 ^k	N=27 ^f	N=28	N=28
Dorsolateral Prostate Weight (g) ^b								
	0.0377	0.0332	0.0390	0.0357	0.0397	0.0371	0.0312	0.0378
	± 0.0017	± 0.0027	± 0.0023	± 0.0024	± 0.0033	± 0.0024	± 0.0030	± 0.0025
	N=56	N=27 ^f	N=28	N=28	N=27 ^l	N=28	N=28	N=28

Table 6. Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 3 of 8)

	Bisphenol A (ppm in the feed)						17β-Estradiol (ppm in the feed)	
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Prostate Weight (g) ^b	0.0725 ± 0.0036 N=56	0.0694 ± 0.0046 N=27 ^m	0.0764 ± 0.0037 N=28	0.0617 ± 0.0043 N=28	0.0719 ± 0.0046 N=27 ^m	0.0693 ± 0.0035 N=27 ^m	0.0616 ± 0.0049 N=28	0.0764 ± 0.0049 N=28
Relative Brain Weight (% of sacrifice weight) ^b	1.3178 ± 0.0180 N=55 ^d	1.3050 ± 0.0259 N=28	1.3300 ± 0.0260 N=28	1.2925 ± 0.0217 N=28	1.2786 ± 0.0195 N=28	1.3086 ± 0.0245 N=28	1.3496 ± 0.0276 N=27 ^c	1.3625 ± 0.0224 N=28
Relative Pituitary Weight (% of sacrifice weight) ^b	0.0069 ††† ± 0.0001 N=54 ^e	0.0067 ± 0.0002 N=28	0.0070 ± 0.0002 N=27 ^e	0.0066 ± 0.0002 N=28	0.0066 ± 0.0002 N=26 ^e	0.0070 ± 0.0002 N=26 ^e	0.0074 ± 0.0002 N=27 ^c	0.0079 *** ± 0.0002 N=28
Relative Thyroid Weight (% of sacrifice weight) ^b	0.0076 ± 0.0002 N=56	0.0072 ± 0.0003 N=27 ^e	0.0077 ± 0.0002 N=26 ^e	0.0075 ± 0.0002 N=27 ^e	0.0081 ± 0.0002 N=27 ^e	0.0080 ± 0.0003 N=27 ^e	0.0081 ± 0.0003 N=26 ^{c,e}	0.0076 ± 0.0002 N=25 ^e
Relative Liver Weight (% of sacrifice weight) ^b	5.4113 ††† ± 0.0561 N=56	5.4068 ± 0.1115 N=28	5.5410 ± 0.0694 N=28	5.4991 ± 0.0791 N=28	5.5700 ± 0.0690 N=28	5.5998 ± 0.0925 N=28	6.3500 *** ± 0.1635 N=27 ^c	5.7691 * ± 0.0801 N=28
Relative Spleen Weight (% of sacrifice weight) ^b	0.2940 ± 0.0091 N=55 ^f	0.2997 ± 0.0214 N=28	0.3102 ± 0.0213 N=28	0.2768 ± 0.0153 N=28	0.2952 ± 0.0131 N=28	0.2959 ± 0.0139 N=28	0.2916 ± 0.0147 N=27 ^c	0.2888 ± 0.0131 N=28
Relative Right Kidney Weight (% of sacrifice weight) ^b	0.9964 ††† ± 0.0137 N=56	0.9816 ± 0.0218 N=28	1.0074 ± 0.0256 N=28	0.9988 ± 0.0178 N=28	1.0198 ± 0.0212 N=28	1.0726 * ± 0.0221 N=28	1.1922 *** ± 0.0239 N=27 ^c	1.0906 ** ± 0.0256 N=28

Table 6. Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 4 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Left Kidney Weight (% of sacrifice weight) ^b	0.9657 ± 0.0139 N=56	0.9483 ± 0.0214 N=28	0.9580 ± 0.0207 N=28	0.9645 ± 0.0211 N=28	1.0000 ± 0.0273 N=28	1.0518 ± 0.0226 N=28	1.1502 ± 0.0196 N=27 ^c	1.0445 ± 0.0221 N=28
Relative Paired Adrenal Gland Weight (% of sacrifice weight) ^b	0.0192 ± 0.0012 N=54 ^g	0.0160 ± 0.0011 N=27 ^f	0.0160 ± 0.0013 N=28	0.0180 ± 0.0018 N=28	0.0168 ± 0.0013 N=27 ^g	0.0175 ± 0.0012 N=28	0.0178 ± 0.0012 N=27 ^c	0.0175 ± 0.0014 N=28
Relative Paired Testis Weight (% of sacrifice weight) ^b	0.6625 ± 0.0130 N=55 ^h	0.6503 ± 0.0154 N=28	0.6993 ± 0.0208 N=28	0.6522 ± 0.0182 N=28	0.6196 ± 0.0202 N=28	0.6752 ± 0.0206 N=28	0.6337 ± 0.0228 N=27 ^c	0.6855 ± 0.0154 N=28
Relative Paired Epididymis Weight (% of sacrifice weight) ^b	0.2928 ± 0.0056 N=56	0.2920 ± 0.0079 N=26 ^{f,i}	0.2915 ± 0.0070 N=28	0.2936 ± 0.0085 N=27 ^l	0.2846 ± 0.0054 N=28	0.2917 ± 0.0083 N=28	0.2854 ± 0.0098 N=27 ^c	0.2972 ± 0.0066 N=28
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight) ^b	0.9787 ± 0.0290 N=56	1.0012 ± 0.0401 N=28	0.9959 ± 0.0422 N=28	1.0368 ± 0.0396 N=28	1.0027 ± 0.0386 N=27 ^j	1.0027 ± 0.0407 N=28	1.0103 ± 0.0500 N=27 ^c	1.0212 ± 0.0466 N=28
Relative Ventral Prostate Weight (% of sacrifice weight) ^b	0.0894 ± 0.0069 N=56	0.0971 ± 0.0100 N=28	0.0959 ± 0.0065 N=28	0.0652 ± 0.0077 N=28	0.0804 ± 0.0061 N=27 ^k	0.0841 ± 0.0077 N=27 ^f	0.0780 ± 0.0079 N=27 ^c	0.1006 ± 0.0104 N=28
Relative Dorsolateral Prostate Weight (% of sacrifice weight) ^b	0.0955 ± 0.0043 N=56	0.0835 ± 0.0071 N=27 ^f	0.0996 ± 0.0060 N=28	0.0886 ± 0.0061 N=28	0.0990 ± 0.0086 N=27 ^l	0.0938 ± 0.0059 N=28	0.0784 ± 0.0080 N=27 ^c	0.0978 ± 0.0065 N=28

Table 6 Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 5 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Prostate Weight (% of sacrifice weight) ^b	0.1849 ± 0.0096 N=58	0.1761 ± 0.0131 N=27 ^m	0.1955 ± 0.0094 N=28	0.1538 ± 0.0116 N=28	0.1794 ± 0.0120 N=27 ^m	0.1770 ± 0.0094 N=27 ^m	0.1565 ± 0.0138 N=27 ^c	0.1984 ± 0.0132 N=28
Relative Pituitary Weight (% of brain weight) ^b	0.5292 ± 0.0124 N=53 ^{d,e}	0.5142 ± 0.0167 N=28	0.5314 ± 0.0175 N=27 ^e	0.5161 ± 0.0174 N=28	0.5204 ± 0.0163 N=26 ^e	0.5413 ± 0.0181 N=26 ^e	0.5521 ± 0.0142 N=28	0.5848 ± 0.0188 N=28
Relative Thyroid Weight (% of brain weight) ^b	0.5805 ± 0.0136 N=55 ^d	0.5495 ± 0.0219 N=27 ^e	0.5838 ± 0.0164 N=26 ^e	0.5831 ± 0.0177 N=27 ^e	0.6306 ± 0.0161 N=27 ^e	0.6107 ± 0.0247 N=27 ^e	0.6020 ± 0.0198 N=27 ^e	0.5607 ± 0.0171 N=25 ^e
Relative Liver Weight (% of brain weight) ^b	413.7071 ††† ± 5.8719 N=55 ^d	416.7152 ± 9.1246 N=28	421.2638 ± 10.2454 N=28	428.3475 ± 8.6703 N=28	437.5957 ± 7.0677 N=28	431.8117 ± 10.3118 N=28	473.5348 *** ± 10.5378 N=28	426.1572 ± 8.6519 N=28
Relative Spleen Weight (% of brain weight) ^b	22.5061 ± 0.7445 N=54 ^{d,f}	22.8156 ± 1.2171 N=28	23.5775 ± 1.6767 N=28	21.4262 ± 1.0717 N=28	23.3049 ± 1.1542 N=28	22.5731 ± 0.9056 N=28	21.8249 ± 0.9630 N=28	21.2266 ± 0.9192 N=28
Relative Right Kidney Weight (% of brain weight) ^b	76.2054 ††† ± 1.2584 N=55 ^d	75.5931 ± 1.6754 N=28	76.1286 ± 1.8016 N=28	77.6607 ± 1.5430 N=28	80.2754 ± 2.0959 N=28	82.4336 * ± 1.8652 N=28	89.1201 *** ± 2.1678 N=28	80.3901 ± 1.9116 N=28
Relative Left Kidney Weight (% of brain weight) ^b	73.7517 ††† ± 1.1270 N=55 ^d	73.2233 ± 1.9350 N=28	72.5302 ± 1.6791 N=28	74.9297 ± 1.6269 N=28	78.7185 ± 2.5489 N=28	80.7555 * ± 1.7501 N=28	86.0672 *** ± 1.9465 N=28	76.9354 ± 1.5738 N=28

Table 6. Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 6 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Paired Adrenal Gland Weight (% of brain weight) ^b	1.4396 ± 0.0812 N=53 ^{d,g}	1.2260 ± 0.0809 N=27 ^f	1.1944 ± 0.0864 N=28	1.3774 ± 0.1216 N=28	1.3204 ± 0.0987 N=27 ^g	1.3447 ± 0.0865 N=28	1.3166 ± 0.0735 N=28	1.2826 ± 0.0969 N=28
Relative Paired Testis Weight (% of brain weight) ^b	50.4263 ± 0.7445 N=54 ^{d,h}	49.9537 ± 0.9479 N=28	52.5526 ± 1.1699 N=28	50.5185 ± 1.2057 N=28	48.6093 ± 1.5866 N=28	51.6849 ± 1.4044 N=28	47.0633 ± 1.6071 N=28	50.4705 ± 1.0997 N=28
Relative Paired Epididymis Weight (% of brain weight) ^b	22.3261 ± 0.3107 N=55 ^d	22.5499 ± 0.4488 N=26 ^{f,i}	21.9656 ± 0.4199 N=28	22.8651 ± 0.5016 N=27 ^l	22.3758 ± 0.5080 N=28	22.3317 ± 0.5342 N=28	21.3220 ± 0.6254 N=28	21.9267 ± 0.5499 N=28
Relative Seminal Vesicles with Coagulating Gland Weight (% of brain weight) ^b	75.1378 ± 2.4889 N=55 ^d	77.7172 ± 3.6516 N=28	75.6333 ± 3.6350 N=28	81.2738 ± 3.9498 N=28	79.3950 ± 3.4344 N=27 ^l	77.3647 ± 3.5167 N=28	76.0386 ± 4.1402 N=28	75.1975 ± 3.3973 N=28
Relative Ventral Prostate Weight (% of brain weight) ^b	6.7053 ± 0.4955 N=55 ^d	7.3777 ± 0.7275 N=28	7.2488 ± 0.4834 N=28	5.0919 ± 0.5873 N=28	6.2571 ± 0.4493 N=27 ^k	6.4612 ± 0.6143 N=27 ^f	5.7091 ± 0.5144 N=28	7.3002 ± 0.7381 N=28
Relative Dorsolateral Prostate Weight (% of brain weight) ^b	7.2564 ± 0.3396 N=55 ^d	6.3669 ± 0.4924 N=27 ^f	7.5297 ± 0.4503 N=28	6.9315 ± 0.4874 N=28	7.7687 ± 0.6724 N=27 ^l	7.2380 ± 0.4887 N=28	5.8610 ± 0.5645 N=28	7.2284 ± 0.5001 N=28
Relative Prostate Weight (% of brain weight) ^b	13.9617 ± 0.6973 N=55 ^d	13.3459 ± 0.8659 N=27 ^m	14.7785 ± 0.6908 N=28	12.0234 ± 0.8882 N=28	14.0257 ± 0.9184 N=27 ^m	13.8089 ± 0.7628 N=27 ^m	11.5702 ± 0.9201 N=28	14.5286 ± 0.9121 N=28

Table 6 Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 7 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Percent Motile Sperm ^b	47.1 ± 1.3 N=56	47.4 ± 1.7 N=28	47.5 ± 2.3 N=28	50.2 ± 1.9 N=28	47.4 ± 1.8 N=28	50.0 ± 1.9 N=28	45.4 ± 2.0 N=28	48.9 ± 2.7 N=28
Percent Progressively Motile Sperm ^b	42.6 ± 1.2 N=56	41.6 ± 1.9 N=28	41.5 ± 2.7 N=28	44.8 ± 1.8 N=28	42.6 ± 1.6 N=28	45.0 ± 1.8 N=28	41.4 ± 1.8 N=28	45.0 ± 2.4 N=28
Epididymal Sperm Concentration (10 ⁶ /g) ^b	1719.27 ††† ± 44.04 N=56	1807.65 ± 53.66 N=28	1706.56 ± 69.02 N=28	1675.69 ± 52.12 N=28	1586.05 ± 48.79 N=28	1838.04 ± 64.37 N=28	1465.23 ** ± 52.45 N=28	1594.17 ± 77.34 N=28
Spermatid Head Concentration (10 ⁶ /g) ^b	196.90 ± 6.40 N=56	189.66 ± 12.40 N=28	210.58 ± 10.92 N=28	200.37 ± 8.43 N=28	216.67 ± 11.08 N=28	182.12 ± 8.40 N=28	187.77 ± 7.23 N=28	190.52 ± 10.69 N=28
Daily Sperm Production per Testis (10 ⁶ /testis/day) ^b	5.39 ± 0.18 N=56	5.23 ± 0.36 N=28	6.02 ± 0.32 N=28	5.55 ± 0.27 N=28	5.78 ± 0.33 N=28	5.06 ± 0.25 N=28	4.99 ± 0.21 N=28	5.27 ± 0.26 N=28
Efficiency of Daily Sperm Production (10 ⁶ /g. testis/day) ^b	40.68 ± 1.32 N=56	39.19 ± 2.56 N=28	43.51 ± 2.26 N=28	41.40 ± 1.74 N=28	44.77 ± 2.29 N=28	37.63 ± 1.74 N=28	38.80 ± 1.49 N=28	39.36 ± 2.21 N=28
Percent Abnormal Sperm ^b	1.71 ± 0.09 N=56	1.60 ± 0.14 N=28	1.53 ± 0.14 N=28	1.56 ± 0.14 N=28	1.72 ± 0.16 N=28	1.43 ± 0.11 N=28	1.68 ± 0.13 N=28	1.56 ± 0.11 N=28

Table 6. Summary and Statistical Analysis of the F₀ Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 8 of 8)

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- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups.
^bReported as the mean \pm S.E M
^cDecrease in N is due to one sacrifice weight inadvertently not being recorded
^dDecrease in N is due to not all of the brain tissue being present at time of weighing.
^eDecrease in N is due to part or all of one or more organs not being present in the tissue cup at the time of weighing the fixed organ
^fDecrease in N is due to one weight being a statistical outlier and, therefore, it was excluded.
^gDecrease in N is due to one of the adrenal glands being lost prior to weighing and, therefore, the paired adrenal gland weight could not be obtained.
^hDecrease in N is due to one of the testes being lost prior to weighing and, therefore, the paired testis weight could not be obtained
ⁱDecrease in N is due to part of one epididymis not being present at the time of weighing and, therefore, the paired epididymis weight could not be obtained.
^jDecrease in N is due to one pair of seminal vesicles being nicked prior to weighing and, therefore, an accurate weight could not be obtained.
^kDecrease in N is due to the ventral prostate for one animal being lost prior to weighing and, therefore, the weight could not be obtained
^lDecrease in N is due to the dorsolateral prostate for one animal being lost prior to weighing and, therefore, the weight could not be obtained
^mDecrease in N is due to either the ventral or dorsolateral prostate weight being missing and, therefore, the total prostate weight could not be calculated.
[#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.
^{††} $p < 0.01$, ANOVA Test
^{†††} $p < 0.001$; ANOVA Test.
^{*} $p < 0.05$, Dunnett's Test.
^{**} $p < 0.01$; Dunnett's Test
^{***} $p < 0.001$, Dunnett's Test
^{††††} $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
^{††} $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model.
^{†††††} $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model.

Table 7 Summary of the F₀ Male Macroscopic and Microscopic Necropsy Findings (page 1 of 4)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Alopecia, above preputial area		1						
back	1							
nose	5	3	1			1	3	2
nose and hip, left							1	
Epididymis: reduced in size, right							2	
Kidney: hydronephrosis, bilateral					1			2
hydronephrosis, left								1
hydronephrosis, right					1	1	1	1
irregular surface and reduced in size, left					1			
pale, bilateral							1	
Lymph Nodes, Cervical enlarged			1					
Penis, abscess, above							1	
Preputial Gland, 3 x 3 mm hard green mass, right						1		
7 x 7 mm mass adjacent to, bilateral	1							
Prostate, Ventral: firm and multiple white nodules		1						
Seminal Vesicles, atrophied, left								1
Sore(s): back							1	
multiple areas		1						
neck			1					
Spleen: enlarged		1	1					
Testis: reduced in size, left							1	
Thymus: enlarged and thickened	1							

Table 7 Summary of the F₀ Male Macroscopic and Microscopic Necropsy Findings (page 2 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>ADRENAL GLAND</u>								
Number Examined	55 ^b	10	10	9	10	10	10	10
Hyperplasia, Spindle Cell	8			1			1	1
<u>COAGULATING GLAND^c</u>								
Number Examined	56	11	11	10	11	14	11	13
No Findings								
<u>EPIDIDYMIS^c</u>								
Number Examined	56	11	11	10	11	14	11	13
Exfoliated Germ Cells			1					
Infiltrative Cell, Mononuclear Cell							1	
<u>KIDNEY</u>								
Number Examined	56	10	10	10	10	10	10	10
Cyst, Cortex	2			1	1			1
Cyst, Medulla								1
Hydronephrosis, Bilateral				1		1		
Hydronephrosis, Unilateral	2	1			1		1	2
Infiltrative Cell, Mononuclear Cell	3		2	1	2	2	1	1
Inflammation, Chronic	2	1				1	1	
Inflammation, Tubulointerstitial, Medulla	3		1		1	2	2	1
Mineralization, Papillae	3	1	1	2			2	
Nephropathy	12		3	2	2	1	4	5
		3	7	7	7	7	11	
<u>LIVER</u>								
Number Examined	56	10	10	10	10	10	10	10
Hypertrophy, Centrilobular, Hepatocyte	6	1	2	2		4	10	
Infiltrative Cell, Mononuclear Cell	5	1	1		1		1	
Necrosis, Hepatocyte, Focal	5	2					1	
Vacuolar Degeneration, Hepatocyte, Centrilobular					1			

Table 7. Summary of the F₀ Male Macroscopic and Microscopic Necropsy Findings (page 3 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>PITUITARY</u>								
Number Examined	54 ^b	10	10	10	10	10	10	10
Cyst, Pars Distalis	1							1
Hyperplasia, Pars Distalis							1	
<u>PREPUTIAL GLAND^d</u>								
Number Examined	1					1		
Abscess	1					1		
<u>PROSTATE, DORSOLATERAL^c</u>								
Number Examined	48 ^b	8 ^b	11	10	10 ^b	14	9 ^b	12 ^b
Infiltrative Cell, Mononuclear Cell	2	1			1			
<u>PROSTATE, VENTRAL^c</u>								
Number Examined	42 ^b	10 ^b	10 ^b	8 ^b	10 ^b	13 ^b	10 ^b	9 ^b
Infiltrative Cell, Mononuclear Cell	2							
<u>SEMINAL VESICLES^c</u>								
Number Examined	56	11	11	10	11	14	11	13
Inflammation, Chronic	1							
<u>SKIN^d</u>								
Number Examined		1						
Ulcer, Epithelium		1						
<u>SKIN, BACK^d</u>								
Number Examined	1							
No Findings								
<u>SKIN, NOSE^d</u>								
Number Examined	4	1				1	1	
Inflammation, Chronic	1							

Table 7 Summary of the F₀ Male Macroscopic and Microscopic Necropsy Findings (page 4 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
SPLEEN								
Number Examined	56	11	10	10	10	10	10	10
Hematopoietic Cell Proliferation	7	2	1	2	2			1
TESTIS^c								
Number Examined	55 ^b	11	11	10	11	14	11	13
Degeneration, Seminiferous Tubule	4	1	1		1	1	1	
THYROID								
Number Examined	56	10	10	10	10	8 ^b	10	10
Cyst, Follicle	2	1			1			
Ectopic Thymus	7	1		2	2			2

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2)

^bThere was not a section of this tissue available for evaluation for one or more males.

^cIncludes males with suspected reduced fertility.

^dIncludes only those males with a macroscopic necropsy finding for this tissue.

Table 18. Summary and Statistical Analysis of F₀ Reproductive and Lactational Indexes for the F₁ Litters (page 1 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. Animals on Study								
Males	56	28	28	28	28	28	28	28
Females	56	28	28	28	28	28	28	28
No. Females Paired	56	28	28	28	28	28	28	28
No. Females that Mated	55	27	27	28	28	28	28	28
Mating Index (no. females that mated/no. females paired)	98.2	96.4	96.4	100.0	100.0	100.0	100.0	100.0
No. of Pregnant Females	55	27	26	28	28	27	28	27
Fertility Index (no. pregnant females/no. females that mated)	100.0	100.0	96.3	100.0	100.0	96.4	100.0	96.4
No. of Females with Live Litters (pnd 0)	51 ^b	27	25 ^c	27 ^d	27 ^e	22 ^f	27 ^g	20 ^h
Gestational Index (no. females with live litters/no. females pregnant)	92.7	100.0	96.2	96.4	96.4	81.5	96.4	74.1
No. Males Paired	56	28	28	28	28	28	28	28
No. Males that Mated	55	27	27	28	28	28	28	28
Mating Index (no. males that mated/no. males paired)	98.2	96.4	96.4	100.0	100.0	100.0	100.0	100.0

Table 18 Summary and Statistical Analysis of F₀ Reproductive and Lactational Indexes for the F₁ Litters (page 2 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. Males Siring Litters	55	27	26	28	28	27	28	27
Fertility Index (no. males siring litters/no. males that mated)	100.0	100.0	96.3	100.0	100.0	96.4	100.0	96.4
Pregnancy Index (no. pregnant females/no. males that mated)	100.0	100.0	96.3	100.0	100.0	96.4	100.0	96.4
Precoital Interval (days) ^{i,j}	2.6 ± 0.2 N=50	2.8 ± 0.4 N=24	2.4 ± 0.2 N=25	2.8 ± 0.5 N=26	1.9 ± 0.1 N=27	2.1 ± 0.2 N=23	2.8 ± 0.4 N=27	2.6 ± 0.5 N=25
Gestational Length (days) ^{i,k} #	19.0 †† ± 0.1 N=49	19.0 ± 0.1 N=24	18.9 ± 0.1 N=24	19.1 ± 0.1 N=26	18.9 ± 0.1 N=27	19.1 ± 0.2 N=21	19.3 ^b ± 0.1 N=27	19.6 ^b ± 0.2 N=24
No. Live Litters								
Postnatal Day 0	51	27	25	27	27	22	27	20
Postnatal Day 4	50 ^l	27	25	26 ^m	26 ⁿ	22	25 ^o	19 ^p
Postnatal Day 7	50	27	25	26	26	22	25	19
Postnatal Day 14	50	27	24 ^q	25 ^r	26	22	24 ^s	19
Postnatal Day 21	50	27	24	25	26	22	24	19
No. Implantation Sites per Litter ^l	12.1 ± 0.3 N=55	11.8 ± 0.4 N=27	12.5 ± 0.5 N=26	13.0 ± 0.3 N=28	12.4 ± 0.5 N=28	11.4 ± 0.7 N=27	12.0 ± 0.5 N=28	11.7 ± 0.5 N=27
Percent Postimplantation Loss per Litter ^l	11.7 ‡ ± 3.6 N=55	2.9 ± 1.0 N=27	8.5 ± 3.0 N=26	8.4 ± 3.2 N=28	6.8 ± 3.6 N=28	17.9 ± 6.5 N=27	5.6 ± 1.5 N=28	19.0 ± 5.6 N=27

Table 18 Summary and Statistical Analysis of F₀ Reproductive and Lactational Indexes for the F₁ Litters (page 3 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Number of Live Pups on Postnatal Day 0 ⁱ	12.5 ^{‡‡} ± 0.3 N=51	12.0 ± 0.4 N=27	11.7 ± 0.7 N=26	11.9 ± 0.7 N=28	12.7 ± 0.5 N=27	11.0 ± 0.8 N=24	11.1 ± 0.7 N=28	8.9 ^{***} ± 1.0 N=25
Number of Dead Pups on Postnatal Day 0 ⁱ #	0.0 [†] ± 0.0 N=51	0.1 ± 0.1 N=27	0.5 ± 0.3 N=26	0.4 ± 0.2 N=28	0.3 ± 0.3 N=27	0.3 ± 0.2 N=24	0.9 ± 0.5 N=28	1.6 [‡] ± 0.7 N=25
Total Number of Pups on Postnatal Day 0 ⁱ	12.5 [‡] ± 0.3 N=51	12.1 ± 0.4 N=27	12.3 ± 0.6 N=26	12.3 ± 0.5 N=28	13.0 ± 0.4 N=27	11.3 ± 0.7 N=24	11.9 ± 0.5 N=28	10.6 [*] ± 0.6 N=25
Stillbirth Index (no. dead on pnd 0/total no. on pnd 0) ⁱ	0.4 ^{‡‡} ± 0.4 N=51	0.9 ± 0.7 N=27	6.2 ± 3.9 N=26	6.0 ± 3.9 N=28	2.9 ± 2.6 N=27	9.5 ± 5.7 N=24	9.1 ± 4.5 N=28	21.5 ^{***} ± 8.1 N=25
Live Birth Index (no. live on pnd 0/total no. on pnd 0) ⁱ	99.6 ^{‡‡} ± 0.4 N=51	99.1 ± 0.7 N=27	93.8 ± 3.9 N=26	94.0 ± 3.9 N=28	97.1 ± 2.6 N=27	90.5 ± 5.7 N=24	90.9 ± 4.5 N=28	78.5 ^{***} ± 8.1 N=25
4 Day Survival Index (no. surviving 4 days/no. live on pnd 0) ⁱ	97.6 ± 2.0 N=51	99.6 ± 0.4 N=27	96.8 ± 2.1 N=25	96.0 ± 3.7 N=27	95.5 ± 3.7 N=27	98.5 ± 0.8 N=22	89.2 ± 5.2 N=27	93.3 ± 5.0 N=20
7 Day Survival Index (no. surviving 7 days/no. live on pnd 4) ⁱ	100.0 ± 0.0 N=50	100.0 ± 0.0 N=27	98.1 ± 1.4 N=25	100.0 ± 0.0 N=26	99.6 ± 0.4 N=26	100.0 ± 0.0 N=22	97.4 ± 2.2 N=25	99.4 ± 0.6 N=19

Table 18 Summary and Statistical Analysis of F₀ Reproductive and Lactational Indexes for the F₁ Litters (page 4 of 5)

	Bisphenol A (ppm in the feed)						17β-Estradiol (ppm in the feed)	
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
14 Day Survival Index (no. surviving 14 days/no. live on pnd 7) ⁱ	100.0	100.0	94.4	100.0	98.8	100.0	94.0	100.0
	± 0.0	± 0.0	± 3.4	± 0.0	± 0.8	± 0.0	± 4.2	± 0.0
	N=50	N=27	N=24	N=25	N=26	N=22	N=25	N=19
21 Day Survival Index (no. surviving 21 days/no. live on pnd 14) ⁱ	99.8	99.6	100.0	99.6	99.1	99.5	100.0	100.0
	± 0.2	± 0.4	± 0.0	± 0.4	± 0.6	± 0.5	± 0.0	± 0.0
	N=50	N=27	N=24	N=25	N=26	N=22	N=24	N=19
Lactational Index (no. surviving 21 days/no. live on pnd 4) ⁱ	99.8	99.6	93.5	99.6	97.7	99.5	93.7	99.4
	± 0.2	± 0.4	± 3.9	± 0.4	± 1.3	± 0.5	± 4.3	± 0.6
	N=50	N=27	N=24	N=25	N=26	N=22	N=25	N=19

Table 18 Summary and Statistical Analysis of F₀ Reproductive and Lactational Indexes for the F₁ Litters (page 5 of 5)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups.
- ^bFemales 96, 184, 230 and 424 were pregnant but had implantation sites only
- ^cFemale 398 was pregnant but had a litter of all dead pups.
- ^dFemale 124 was pregnant but had a litter of all dead pups.
- ^eFemale 206 was pregnant but had implantation sites only.
- ^fFemales 436, 466 and 490 were pregnant but had implantation sites only Females 148 and 244 were pregnant but had litters of all dead pups
- ^gFemale 404 was pregnant but had a litter of all dead pups.
- ^hFemales 350 and 408 were pregnant but had implantation sites only. Females 86, 142, 290, 312 and 382 were pregnant but had litters of all dead pups.
- ⁱReported as the mean \pm S.E.M.; pnd=postnatal day All indexes are the average percent per litter.
- ^jPrecoital interval could only be calculated for those females for which a plug was detected
- ^kGestational length could not be calculated for females that were pregnant, but for which a plug was never detected.
- ^lThe entire litter for female 308 was found dead or missing and presumed dead on or before postnatal day 2.
- ^mThe entire litter for female 272 was found dead or missing and presumed dead on or before postnatal day 3.
- ⁿThe entire litter for female 22 was found dead or missing and presumed dead on or before postnatal day 1
- ^oThe entire litter for female 116 was found dead or missing and presumed dead on or before postnatal day 2 and the entire litter for female 438 was found dead or missing and presumed dead on or before postnatal day 4.
- ^pThe entire litter for female 198 was found dead or missing and presumed dead on the afternoon of postnatal day 0.
- ^qFemale 368 was found dead on postnatal day 11 and, therefore, her litter was euthanized on postnatal day 11.
- ^rFemale 14 was found dead on postnatal day 14 and, therefore, her litter was euthanized on postnatal day 14.
- ^sThe entire litter for female 372 was found dead or missing and presumed dead on or before postnatal day 9
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.
- ^{££} $p < 0.05$; Chi-Square Test.
- [†] $p < 0.05$; Wald Chi-square Test for overall treatment effect in robust regression model.
- ^{††} $p < 0.05$; Wald Chi-square Test for overall treatment effect in robust regression model
- ^P $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model.
- [‡] $p < 0.05$; ANOVA Test or ANOVA Test weighted for litter size
- ^{‡‡} $p < 0.01$; ANOVA Test or ANOVA Test weighted for litter size.
- ^{*} $p < 0.05$; Dunnett's Test.
- ^{***} $p < 0.001$; Dunnett's Test

Table 19 Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

(page 1 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No Live Litters								
Postnatal Day 0	51	27	25	27	27	22	27	20
Postnatal Day 4	50 ^b	27	25	26 ^c	26 ^d	22	25 ^e	19 ^f
Postnatal Day 7	50	27	25	26	26	22	25	19
Postnatal Day 14	50	27	24 ^g	25 ^h	26	22	24 ⁱ	19
Postnatal Day 21	50	27	24	25	26	22	24	19
Average Number of Live Pups per Litter (pnd 0) ^j	12.5 ± 0.3 N=51	12.0 ± 0.4 N=27	12.2 ± 0.5 N=25	12.3 ± 0.5 N=27	12.7 ± 0.5 N=27	12.0 ± 0.5 N=22	11.5 ± 0.6 N=27	11.2 ± 0.5 N=20
Average Number of Live Pups per Litter (pnd 4) ^j	12.4 ± 0.3 N=50	12.0 ± 0.4 N=27	11.8 ± 0.6 N=25	12.2 ± 0.5 N=26	13.0 ± 0.4 N=26	11.8 ± 0.4 N=22	11.8 ± 0.5 N=25	10.8 ± 0.5 N=19
Average Number of Live Pups per Litter (pnd 7) ^j	9.7 ± 0.1 N=50	9.8 ± 0.1 N=27	9.3 ± 0.4 N=25	9.6 ± 0.3 N=26	9.8 ± 0.1 N=26	9.7 ± 0.2 N=22	9.4 ± 0.3 N=25	9.5 ± 0.2 N=19
Average Number of Live Pups per Litter (pnd 14) ^j	# 9.7 ± 0.1 N=50	9.8 ± 0.1 N=27	8.8 ± 0.5 N=24	9.6 ± 0.3 N=25	9.7 ± 0.1 N=26	9.7 ± 0.2 N=22	9.5 ± 0.3 N=24	9.5 ± 0.2 N=19
Average Number of Live Pups per Litter (pnd 21) ^j	# 9.7 ± 0.1 N=50	9.7 ± 0.1 N=27	8.8 ± 0.5 N=24	9.6 ± 0.3 N=25	9.7 ± 0.1 N=26	9.6 ± 0.2 N=22	9.5 ± 0.3 N=24	9.5 ± 0.2 N=19

Table 19 Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

(page 2 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Average Male Pup Anogenital Distance (mm) per Litter (pnd 0)^j								
	1.42	1.48	1.43	1.32	1.31	1.40	1.42	1.43
	± 0.05	± 0.06	± 0.06	± 0.05	± 0.05	± 0.07	± 0.06	± 0.07
	N=51	N=27	N=25	N=27	N=27	N=22	N=27	N=20
Average Adjusted Male Pup Anogenital Distance (mm) per Litter (pnd 0)^k								
	1.42	1.48	1.43	1.32	1.32	1.40	1.43	1.43
	± 0.04	± 0.06	± 0.06	± 0.06	± 0.06	± 0.07	± 0.06	± 0.07
	N=51	N=27	N=25	N=27	N=27	N=22	N=27	N=20
Average Female Pup Anogenital Distance (mm) per Litter (pnd 0)^j								
	0.74	0.78	0.77	0.71	0.71	0.75	0.75	0.77
	± 0.03	± 0.04	± 0.04	± 0.04	± 0.03	± 0.04	± 0.04	± 0.04
	N=51	N=27	N=25	N=27	N=27	N=22	N=25 ^l	N=20
Average Adjusted Female Pup Anogenital Distance (mm) per Litter (pnd 0)^k								
	0.74	0.78	0.77	0.71	0.71	0.75	0.75	0.77
	± 0.03	± 0.04	± 0.04	± 0.04	± 0.04	± 0.04	± 0.04	± 0.04
	N=51	N=27	N=25	N=27	N=27	N=22	N=25 ^l	N=20
Average Pup Body Weight (g) per Litter (pnd 0)^j								
	1.59	1.61	1.60	1.65	1.56	1.61	1.58	1.68
	± 0.02	± 0.02	± 0.03	± 0.03	± 0.04	± 0.03	± 0.04	± 0.03
	N=51	N=27	N=25	N=27	N=27	N=22	N=27	N=20
Average Male Body Weight (g) per Litter (pnd 0)^j								
	1.63	1.65	1.66	1.69	1.58	1.65	1.61	1.71
	± 0.02	± 0.02	± 0.03	± 0.03	± 0.04	± 0.03	± 0.04	± 0.03
	N=51	N=27	N=25	N=27	N=27	N=22	N=27	N=20
Average Female Body Weight (g) per Litter (pnd 0)^j								
	1.56	1.58	1.57	1.62	1.55	1.57	1.53	1.64
	± 0.02	± 0.02	± 0.03	± 0.03	± 0.03	± 0.03	± 0.03	± 0.04
	N=51	N=27	N=25	N=27	N=27	N=22	N=25 ^l	N=20

Table 19 Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

(page 3 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Average Pup Body Weight (g) per Litter (pnd 4) ^l	2.88 ‡ ± 0.05 N=50	2.98 ± 0.06 N=27	2.88 ± 0.11 N=25	3.00 ± 0.08 N=26	2.91 ± 0.08 N=26	2.94 ± 0.08 N=22	2.63 ± 0.10 N=25	3.12 ± 0.09 N=19
Average Male Body Weight (g) per Litter (pnd 4) ^l	2.94 ‡ ± 0.05 N=50	3.03 ± 0.06 N=27	2.98 ± 0.11 N=25	3.07 ± 0.08 N=26	2.95 ± 0.08 N=26	3.00 ± 0.08 N=22	2.69 ± 0.10 N=25	3.16 ± 0.09 N=19
Average Female Body Weight (g) per Litter (pnd 4) ^l	2.82 ‡ ± 0.05 N=50	2.92 ± 0.06 N=27	2.82 ± 0.11 N=25	2.93 ± 0.08 N=26	2.85 ± 0.08 N=26	2.89 ± 0.09 N=22	2.56 ± 0.10 N=25	3.07 ± 0.09 N=19
Average Pup Body Weight (g) per Litter (pnd 7) ^j	4.71 ‡‡‡ ± 0.08 N=50	4.86 ± 0.08 N=27	4.75 ± 0.17 N=25	4.94 ± 0.10 N=26	4.86 ± 0.13 N=26	4.89 ± 0.10 N=22	4.09 *** ± 0.18 N=25	4.74 ± 0.12 N=19
Average Male Body Weight (g) per Litter (pnd 7) ^j #	4.76 †† ± 0.08 N=50	4.92 ± 0.07 N=27	4.87 ± 0.19 N=25	5.02 ▽ ± 0.10 N=26	4.93 ± 0.13 N=26	4.97 ± 0.10 N=22	4.15 †† ± 0.17 N=25	4.81 ± 0.12 N=19
Average Female Body Weight (g) per Litter (pnd 7) ^j	4.67 ‡‡‡ ± 0.08 N=50	4.81 ± 0.08 N=27	4.67 ± 0.18 N=25	4.86 ± 0.10 N=26	4.79 ± 0.12 N=26	4.81 ± 0.10 N=22	4.01 *** ± 0.19 N=25	4.67 ± 0.11 N=19

Table 19. Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

(page 4 of 6)

	Bisphenol A (ppm in the feed)						17β-Estradiol	
	0 ^a	0.018	0.18	1.8	30	300	(ppm in the feed)	
						3500	0.5	
Average Pup Body Weight (g) per Litter (pnd 14) ^j	7.48 ‡ ± 0.13 N=50	7.55 ± 0.15 N=27	7.33 ± 0.29 N=24	7.65 ± 0.23 N=25	7.42 ± 0.18 N=26	7.49 ± 0.19 N=22	6.68 * ± 0.21 N=24	7.30 ± 0.21 N=19
Average Male Body Weight (g) per Litter (pnd 14) ^j	7.50 ± 0.13 N=50	7.61 ± 0.14 N=27	7.48 ± 0.31 N=24	7.70 ± 0.23 N=25	7.46 ± 0.18 N=26	7.58 ± 0.19 N=22	6.77 ± 0.20 N=24	7.32 ± 0.21 N=19
Average Female Body Weight (g) per Litter (pnd 14) ^j	7.46 ‡ ± 0.13 N=50	7.50 ± 0.15 N=27	7.23 ± 0.30 N=24	7.61 ± 0.23 N=25	7.37 ± 0.18 N=26	7.40 ± 0.20 N=22	6.57 ** ± 0.21 N=24	7.29 ± 0.21 N=19
Average Pup Body Weight (g) per Litter (pnd 21) ^j	10.67 ††† ± 0.22 N=50	10.89 ± 0.22 N=27	10.67 ± 0.44 N=24	10.93 ± 0.39 N=25	10.87 ± 0.29 N=26	11.01 ± 0.33 N=22	8.89 *** ± 0.34 N=24	10.77 ± 0.40 N=19
Average Male Body Weight (g) per Litter (pnd 21) ^j	10.89 ††† ± 0.23 N=50	11.11 ± 0.23 N=27	11.06 ± 0.49 N=24	11.17 ± 0.41 N=25	11.15 ± 0.31 N=26	11.32 ± 0.34 N=22	9.12 *** ± 0.34 N=24	10.88 ± 0.40 N=19
Average Female Body Weight (g) per Litter (pnd 21) ^j	10.48 ††† ± 0.22 N=50	10.64 ± 0.20 N=27	10.38 ± 0.43 N=24	10.70 ± 0.38 N=25	10.56 ± 0.28 N=26	10.67 ± 0.33 N=22	8.60 *** ± 0.35 N=24	10.63 ± 0.42 N=19

Table 19. Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

(page 5 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Percent Male Pups per Litter (pnd 0) ^j								
#	48.4	53.0	50.0	52.4	53.9	57.2	52.9	54.8
	+2.1	+2.3	+2.9	+2.4	+2.4	+3.7	+3.9	+3.7
	N=51	N=27	N=25	N=27	N=27	N=22	N=27	N=20
Percent Male Pups per Litter (pnd 4) ^j								
	49.2	52.9	51.0	52.7	53.2	56.4	50.5	54.9
	+2.1	+2.3	+3.2	+2.5	+2.5	+3.8	+3.1	+4.0
	N=50	N=27	N=25	N=26	N=26	N=22	N=25	N=19
Percent Male Pups per Litter (pnd 7) ^j								
	49.9	50.9	50.9	51.4	52.5	56.2	48.2	55.4
	+1.5	+1.6	+2.6	+1.8	+1.4	+2.9	+2.2	+3.6
	N=50	N=27	N=25	N=26	N=26	N=22	N=25	N=19
Percent Male Pups per Litter (pnd 14) ^j								
	49.7	50.9	49.1	51.0	52.7	56.2	47.8	55.4
	+1.5	+1.6	+2.6	+1.8	+1.4	+2.9	+2.7	+3.6
	N=50	N=27	N=24	N=25	N=26	N=22	N=24	N=19
Percent Male Pups per Litter (pnd 21) ^j								
	49.8	51.1	49.1	51.3	52.7	55.9	47.8	55.4
	+1.5	+1.6	+2.6	+1.8	+1.5	+2.9	+2.7	+3.6
	N=50	N=27	N=24	N=25	N=26	N=22	N=24	N=19

Table 19 Summary and Statistical Analysis of the F₁ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation

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- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups
- ^bThe entire litter for female 308 was found dead or missing and presumed dead on or before postnatal day 2.
- ^cThe entire litter for female 272 was found dead or missing and presumed dead on or before postnatal day 3.
- ^dThe entire litter for female 22 was found dead or missing and presumed dead on or before postnatal day 1.
- ^eThe entire litter for female 116 was found dead or missing and presumed dead on or before postnatal day 2 and the entire litter for female 438 was found dead or missing and presumed dead on or before postnatal day 4.
- ^fThe entire litter for female 198 was found dead or missing and presumed dead on the afternoon of postnatal day 0.
- ^gFemale 368 was found dead on postnatal day 11 and, therefore, her litter was euthanized on postnatal day 11
- ^hFemale 14 was found dead on postnatal day 14 and, therefore, her litter was euthanized on postnatal day 14
- ⁱThe entire litter for female 372 was found dead or missing and presumed dead on or before postnatal day 9
- ^jReported as the mean \pm S.E.M.; pnd=postnatal day.
- ^kReported as the adjusted mean \pm S.E.M. (body weight as covariate).
- ^lDecrease in N is due to one or more litters having only male pups.
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects
- [†] $p < 0.05$; ANOVA Test
- ^{†††} $p < 0.001$; ANOVA Test
- ^{*} $p < 0.05$; Dunnett's Test.
- ^{**} $p < 0.01$; Dunnett's Test
- ^{***} $p < 0.001$; Dunnett's Test
- ^{††} $p < 0.01$, Wald Chi-square Test for overall treatment effect in robust regression model.
- ^p $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model
- ^{pp} $p < 0.01$; Individual t-test for pairwise comparisons to control in robust regression model.

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 1 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. F₁ Male Pups Necropsied with Organ Weights^b	92	53	37	44	50	42	41	34
Total No. F₁ Male Pups Necropsied^b	135	79	54	70	78	68	56	53
Sacrifice Body Weight (g)^c	10.53 $\Gamma\Gamma$ ± 0.23 N=135	10.94 ± 0.21 N=78 ^d	10.84 ± 0.40 N=54	10.60 ± 0.32 N=70	10.86 ± 0.30 N=78	10.85 ± 0.30 N=68	9.22 $\delta\delta\delta$ ± 0.33 N=56	10.19 ± 0.65 N=53
Anogenital Distance (mm)^c	7.4 $\Gamma\Gamma\Gamma$ ± 0.1 N=135	7.3 ± 0.2 N=79	7.2 ± 0.2 N=54	7.2 ± 0.2 N=70	7.4 ± 0.2 N=78	7.1 ± 0.2 N=68	6.3 $\delta\delta\delta$ ± 0.2 N=56	6.3 $\delta\delta$ ± 0.3 N=53
Adjusted Anogenital Distance (mm)^e	7.3 $\Gamma\Gamma\Gamma$ ± 0.1 N=135	7.1 ± 0.1 N=78 ^d	7.1 ± 0.1 N=54	7.2 ± 0.1 N=70	7.3 ± 0.1 N=78	7.0 θ ± 0.1 N=68	6.9 $\theta\theta$ ± 0.1 N=56	6.5 $\theta\theta\theta$ ± 0.1 N=53
Brain Weight (g)^c	0.4398 ± 0.0033 N=90 ^f	0.4437 ± 0.0039 N=53	0.4453 ± 0.0059 N=36 ^f	0.4471 ± 0.0063 N=43 ^f	0.4491 ± 0.0045 N=49 ^f	0.4421 ± 0.0066 N=41 ^f	0.4162 ± 0.0105 N=40 ^f	0.4328 ± 0.0087 N=34
Thymus Weight (g)^c	0.0668 Γ ± 0.0021 N=92	0.0720 ± 0.0033 N=53	0.0723 ± 0.0037 N=37	0.0689 ± 0.0034 N=44	0.0722 ± 0.0028 N=50	0.0785 $\delta\delta$ ± 0.0034 N=42	0.0625 ± 0.0037 N=41	0.0629 ± 0.0045 N=34
Liver Weight (g)^c	0.5564 ± 0.0129 N=92	0.5962 ± 0.0155 N=53	0.5774 ± 0.0298 N=37	0.5678 ± 0.0244 N=44	0.5753 ± 0.0182 N=50	0.6088 ± 0.0275 N=42	0.4907 ± 0.0281 N=41	0.5523 ± 0.0313 N=34

Table 22 Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 2 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Spleen Weight (g) ^c	0.0793 ΓΓΓ ± 0.0029 N=92	0.0769 ± 0.0043 N=53	0.0707 ± 0.0046 N=37	0.0775 ± 0.0053 N=44	0.0783 ± 0.0046 N=50	0.0842 ± 0.0051 N=42	0.0484 δδδ ± 0.0046 N=41	0.0667 ± 0.0060 N=34
Right Kidney Weight (g) ^c	0.0931 ± 0.0018 N=92	0.0979 ± 0.0028 N=53	0.0977 ± 0.0044 N=37	0.0986 ± 0.0043 N=44	0.0974 ± 0.0034 N=50	0.1011 ± 0.0043 N=42	0.0865 ± 0.0050 N=41	0.0931 ± 0.0055 N=34
Left Kidney Weight (g) ^c	0.0902 ± 0.0019 N=92	0.0940 ± 0.0032 N=53	0.0947 ± 0.0047 N=36 ^g	0.0951 ± 0.0046 N=43 ^g	0.0944 ± 0.0033 N=50	0.0966 ± 0.0047 N=41 ^f	0.0838 ± 0.0049 N=41	0.0907 ± 0.0052 N=34
Paired Testis Weight (g) ^c	0.0534 ΓΓΓ ± 0.0014 N=90 ^{f,g}	0.0547 ± 0.0016 N=53	0.0546 ± 0.0026 N=37	0.0561 ± 0.0030 N=44	0.0559 ± 0.0026 N=49 ^f	0.0570 ± 0.0028 N=42	0.0426 δδδ ± 0.0026 N=41	0.0394 δδδ ± 0.0026 N=34
Paired Epididymis Weight (g) ^c	0.0181 ΓΓΓ ± 0.0006 N=92	0.0190 ± 0.0009 N=53	0.0220 δ ± 0.0016 N=37	0.0188 ± 0.0011 N=43 ^f	0.0202 ± 0.0012 N=50	0.0185 ± 0.0009 N=41 ^f	0.0164 ± 0.0010 N=41	0.0145 δδ ± 0.0009 N=34
Seminal Vesicles with Coagulating Gland Weight (g) ^c	0.0084 Γ ± 0.0005 N=92	0.0083 ± 0.0005 N=50 ^f	0.0101 ± 0.0013 N=36 ^g	0.0096 ± 0.0009 N=43 ^f	0.0098 ± 0.0006 N=50	0.0105 δ ± 0.0009 N=41 ^g	0.0075 ± 0.0007 N=41	0.0074 ± 0.0007 N=33 ^g
Relative Brain Weight (% of sacrifice weight) ^c	4.2350 ± 0.0850 N=90 ^f	4.0914 ± 0.0668 N=53	4.1969 ± 0.1312 N=36 ^f	4.3459 ± 0.1611 N=43 ^f	4.2359 ± 0.1092 N=49 ^f	4.1200 ± 0.1189 N=41 ^f	4.7924 ± 0.2091 N=40 ^f	4.2294 ± 0.1830 N=34

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 3 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% of sacrifice weight) ^c	0.6284 Γ ± 0.0148 N=92	0.6536 ± 0.0247 N=53	0.6717 ± 0.0233 N=37	0.6469 ± 0.0196 N=44	0.6679 ± 0.0191 N=50	0.7125 $\delta\delta$ ± 0.0238 N=42	0.6881 δ ± 0.0245 N=41	0.5838 ± 0.0258 N=34
Relative Liver Weight (% of sacrifice weight) ^c	5.2437 ± 0.0646 N=92	5.4372 ± 0.0689 N=53	5.3124 ± 0.1019 N=37	5.3053 ± 0.0947 N=44	5.3017 ± 0.0695 N=50	5.5154 ± 0.1421 N=42	5.3652 ± 0.1189 N=41	5.1710 ± 0.1307 N=34
Relative Spleen Weight (% of sacrifice weight) ^c	0.7364 $\Gamma\Gamma\Gamma$ ± 0.0211 N=92	0.6948 ± 0.0339 N=53	0.6494 δ ± 0.0315 N=37	0.7122 ± 0.0345 N=44	0.7069 ± 0.0288 N=50	0.7547 ± 0.0353 N=42	0.5173 $\delta\delta\delta$ ± 0.0334 N=41	0.6118 δ ± 0.0402 N=34
Relative Right Kidney Weight (% of sacrifice weight) ^c	0.8830 ± 0.0115 N=92	0.8951 ± 0.0204 N=53	0.9053 ± 0.0172 N=37	0.9285 ± 0.0207 N=44	0.8973 ± 0.0172 N=50	0.9307 ± 0.0401 N=42	0.9503 ± 0.0248 N=41	0.8781 ± 0.0334 N=34
Relative Left Kidney Weight (% of sacrifice weight) ^c	0.8541 ± 0.0121 N=92	0.8584 ± 0.0242 N=53	0.8677 ± 0.0220 N=36 ^g	0.8961 ± 0.0244 N=43 ^g	0.8703 ± 0.0177 N=50	0.8947 ± 0.0476 N=41 ^f	0.9179 ± 0.0231 N=41	0.8535 ± 0.0284 N=34
Relative Paired Testis Weight (% of sacrifice weight) ^c	0.5022 $\Gamma\Gamma\Gamma$ ± 0.0076 N=90 ^{f,g}	0.5001 ± 0.0125 N=53	0.5045 ± 0.0104 N=37	0.5225 ± 0.0149 N=44	0.5090 ± 0.0135 N=49 ^f	0.5131 ± 0.0155 N=42	0.4640 δ ± 0.0151 N=41	0.3702 $\delta\delta\delta$ ± 0.0167 N=34
Relative Paired Epididymis Weight (% of sacrifice weight) ^c	0.1722 $\Gamma\Gamma\Gamma$ ± 0.0053 N=92	0.1740 ± 0.0082 N=53	0.2032 δ ± 0.0116 N=37	0.1761 ± 0.0069 N=43 ^f	0.1860 ± 0.0094 N=50	0.1705 ± 0.0087 N=41 ^f	0.1813 ± 0.0072 N=41	0.1389 $\delta\delta$ ± 0.0086 N=34
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight) ^c	0.0797 ± 0.0046 N=92	0.0768 ± 0.0048 N=50 ^f	0.0913 ± 0.0098 N=36 ^g	0.0900 ± 0.0072 N=43 ^f	0.0900 ± 0.0044 N=50	0.0948 ± 0.0085 N=41 ^g	0.0820 ± 0.0059 N=41	0.0710 ± 0.0066 N=33 ^g

Table 22 Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 4 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% of brain weight) ^c	15.0654 ± 0.4427 N=90 ^h	16.1747 ± 0.7051 N=53	16.3284 ± 0.7534 N=36 ^h	15.2672 ± 0.8692 N=43 ^h	15.9860 ± 0.5752 N=49 ^h	17.4752 ± 0.6678 N=41 ^h	14.8727 ± 0.8331 N=40 ^h	14.3576 ± 0.9293 N=34
Relative Liver Weight (% of brain weight) ^c	126.6286 ± 2.6858 N=90 ^h	134.1881 ± 3.0016 N=53	130.3678 ± 5.5732 N=36 ^h	126.3179 ± 4.6253 N=43 ^h	127.6396 ± 3.6231 N=49 ^h	137.5657 ± 6.1603 N=41 ^h	116.8337 ± 5.5248 N=40 ^h	126.1865 ± 5.7344 N=34
Relative Spleen Weight (% of brain weight) ^c	17.9832 ΓΓΓ ± 0.6134 N=90 ^h	17.2234 ± 0.9018 N=53	15.8189 δ ± 0.9244 N=36 ^h	17.0752 ± 1.0464 N=43 ^h	17.3173 ± 0.9988 N=49 ^h	18.5324 ± 1.1197 N=41 ^h	11.3019 δδδ ± 0.9015 N=40 ^h	15.1267 ± 1.1844 N=34
Relative Right Kidney Weight (% of brain weight) ^c	21.2024 ± 0.3748 N=90 ^h	22.0257 ± 0.5703 N=53	22.0416 ± 0.8536 N=36 ^h	21.9280 ± 0.7653 N=43 ^h	21.5419 ± 0.6765 N=49 ^h	23.0501 ± 0.7504 N=41 ^h	20.5867 ± 1.0565 N=40 ^h	21.2137 ± 0.9113 N=34
Relative Left Kidney Weight (% of brain weight) ^c	20.4694 ± 0.3708 N=90 ^h	21.1379 ± 0.6494 N=53	21.3656 ± 0.9234 N=35 ^{g,h}	21.0520 ± 0.8084 N=42 ^{g,h}	20.8961 ± 0.6413 N=49 ^h	21.9871 ± 0.8926 N=40 ^{f,h}	19.9049 ± 1.0025 N=40 ^h	20.6721 ± 0.8705 N=34
Relative Paired Testis Weight (% of brain weight) ^c	12.1241 ΓΓΓ ± 0.2716 N=88 ^{f,g,h}	12.3049 ± 0.3134 N=53	12.3326 ± 0.4597 N=36 ^h	12.4266 ± 0.5775 N=43 ^h	12.3565 ± 0.5350 N=48 ^{f,h}	12.7743 ± 0.5873 N=41 ^h	10.1285 δδ ± 0.5915 N=40 ^h	9.0016 δδδ ± 0.5128 N=34
Relative Paired Epididymis Weight (% of brain weight) ^c	4.1158 ΓΓΓ ± 0.1306 N=90 ^h	4.2708 ± 0.2018 N=53	4.9294 δ ± 0.3363 N=36 ^h	4.1439 ± 0.2117 N=42 ^{f,h}	4.4815 ± 0.2675 N=49 ^h	4.2141 ± 0.2243 N=40 ^{f,h}	3.9039 ± 0.2279 N=40 ^h	3.3247 δδδ ± 0.1902 N=34

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 5 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Relative Seminal Vesicles with Coagulating Gland Weight (% of brain weight) ^c	1.9047 Γ ± 0.1031 N=90 ^h	1.8711 ± 0.1116 N=50 ^f	2.2487 ± 0.2600 N=359 ^h	2.1292 ± 0.1961 N=42 ^{f,h}	2.1975 ± 0.1284 N=49 ^h	2.3693 δ ± 0.2107 N=409 ^h	1.7403 ± 0.1403 N=40 ^h	1.7124 ± 0.1650 N=339
No. F₁ Female Pups Necropsied with Organ Weights	96	54	41	49	51	38	45	32
Total No. F₁ Female Pups Necropsied^b	187	100 ⁱ	80	88	91	66	92	52
Sacrifice Body Weight (g) ^c	10.34 $\Gamma\Gamma\Gamma$ ± 0.21 N=187	10.43 ± 0.21 N=100	10.36 ± 0.26 N=80	10.30 ± 0.32 N=88	10.49 ± 0.30 N=91	10.31 ± 0.28 N=66	8.46 $\delta\delta\delta$ ± 0.40 N=92	11.03 ± 0.28 N=52
Anogenital Distance (mm) ^c	4.5 ± 0.1 N=187	4.6 ± 0.1 N=100	4.5 ± 0.1 N=80	4.5 ± 0.1 N=88	4.6 ± 0.1 N=91	4.5 ± 0.1 N=66	4.1 ± 0.1 N=92	4.6 ± 0.1 N=52
Adjusted Anogenital Distance (mm) ^e	4.5 ± 0.0 N=187	4.5 ± 0.1 N=100	4.5 ± 0.1 N=80	4.5 ± 0.1 N=88	4.6 ± 0.1 N=91	4.5 ± 0.1 N=66	4.6 ± 0.1 N=92	4.4 ± 0.1 N=52
Brain Weight (g) ^c	0.4395 ± 0.0042 N=94 ^f	0.4382 ± 0.0046 N=54	0.4378 ± 0.0081 N=40 ^f	0.4285 ± 0.0093 N=48 ^f	0.4412 ± 0.0050 N=51	0.4303 ± 0.0046 N=37 ^f	0.4196 ± 0.0064 N=45	0.4439 ± 0.0052 N=32
Thymus Weight (g) ^c	0.0688 ± 0.0025 N=96	0.0727 ± 0.0029 N=53 ^f	0.0740 ± 0.0043 N=41	0.0729 ± 0.0035 N=49	0.0713 ± 0.0030 N=51	0.0722 ± 0.0043 N=38	0.0604 ± 0.0049 N=45	0.0692 ± 0.0056 N=32

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 6 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Liver Weight (g) ^c	0.5446 ± 0.0150 N=96	0.5751 ± 0.0155 N=54	0.5550 ± 0.0215 N=41	0.5689 ± 0.0232 N=49	0.5534 ± 0.0191 N=51	0.5581 ± 0.0244 N=38	0.4718 ± 0.0279 N=45	0.5771 ± 0.0207 N=32
Spleen Weight (g) ^c	0.0790 Γ ± 0.0032 N=96	0.0748 ± 0.0040 N=54	0.0724 ± 0.0046 N=41	0.0753 ± 0.0053 N=49	0.0784 ± 0.0044 N=51	0.0760 ± 0.0063 N=38	0.0525 δδδ ± 0.0058 N=45	0.0715 ± 0.0044 N=32
Right Kidney Weight (g) ^c	0.0949 ± 0.0024 N=96	0.0973 ± 0.0026 N=53 ^f	0.0956 ± 0.0041 N=41	0.0986 ± 0.0040 N=49	0.0975 ± 0.0037 N=51	0.0991 ± 0.0039 N=38	0.0878 ± 0.0053 N=45	0.1012 ± 0.0042 N=32
Left Kidney Weight (g) ^c	0.0914 ± 0.0023 N=96	0.0946 ± 0.0027 N=53 ^f	0.0915 ± 0.0038 N=41	0.0952 ± 0.0039 N=49	0.0948 ± 0.0036 N=51	0.0961 ± 0.0040 N=38	0.0855 ± 0.0050 N=45	0.0977 ± 0.0037 N=32
Paired Ovary Weight (g) ^c	0.0092 ΓΓΓ ± 0.0003 N=95 ^f	0.0102 ± 0.0005 N=53 ^g	0.0101 ± 0.0005 N=41	0.0110 δδ ± 0.0006 N=49 ^g	0.0103 ± 0.0005 N=49	0.0098 ± 0.0005 N=38	0.0084 ± 0.0006 N=45	0.0129 δδδ ± 0.0008 N=32
Uterus with Cervix and Vagina Weight (g) ^c	0.0451 ΓΓΓ ± 0.0028 N=96	0.0493 ± 0.0032 N=54	0.0543 ± 0.0046 N=41	0.0478 ± 0.0045 N=49	0.0455 ± 0.0032 N=51	0.0469 ± 0.0036 N=38	0.0413 ± 0.0034 N=45	0.2058 δδδ ± 0.0154 N=32
Relative Brain Weight (% sacrifice weight) ^c	4.3498 ΓΓ ± 0.0790 N=94 ^f	4.1841 ± 0.0781 N=54	4.2899 ± 0.1027 N=40 ^f	4.1654 ± 0.1088 N=48 ^f	4.2935 ± 0.1278 N=51	4.2909 ± 0.1272 N=37 ^f	5.0922 δδ ± 0.2084 N=45	4.0609 δ ± 0.1029 N=32

Table 22 Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 7 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% sacrifice weight) ^C	0.6638 ± 0.0173 N=96	0.6832 ± 0.0200 N=53 ^f	0.7144 ± 0.0334 N=41	0.6855 ± 0.0184 N=49	0.6748 ± 0.0208 N=51	0.6959 ± 0.0281 N=38	0.6799 ± 0.0396 N=45	0.6189 ± 0.0389 N=32
Relative Liver Weight (% sacrifice weight) ^C	5.2552 ± 0.0696 N=96	5.4163 ± 0.0754 N=54	5.3458 ± 0.0663 N=41	5.3700 ± 0.0859 N=49	5.2411 ± 0.0782 N=51	5.4041 ± 0.1126 N=38	5.4141 ± 0.1312 N=45	5.1957 ± 0.0839 N=32
Relative Spleen Weight (% sacrifice weight) ^C	0.7488 Γ ± 0.0217 N=96	0.6987 ± 0.0331 N=54	0.6879 ± 0.0323 N=41	0.7003 ± 0.0379 N=49	0.7282 ± 0.0300 N=51	0.7220 ± 0.0489 N=38	0.5733 $\delta\delta$ ± 0.0464 N=45	0.6379 $\delta\delta$ ± 0.0302 N=32
Relative Right Kidney Weight (% sacrifice weight) ^C	0.9187 ± 0.0129 N=96	0.9205 ± 0.0182 N=53 ^f	0.9254 ± 0.0219 N=41	0.9396 ± 0.0227 N=49	0.9230 ± 0.0182 N=51	0.9678 ± 0.0304 N=38	1.0092 ± 0.0315 N=45	0.9109 ± 0.0244 N=32
Relative Left Kidney Weight (% sacrifice weight) ^C	0.8854 ± 0.0129 N=96	0.8949 ± 0.0193 N=53 ^f	0.8850 ± 0.0180 N=41	0.9063 ± 0.0228 N=49	0.8979 ± 0.0180 N=51	0.9391 ± 0.0322 N=38	0.9858 ± 0.0297 N=45	0.8808 ± 0.0231 N=32
Relative Paired Ovary Weight (% sacrifice weight) ^C	0.0904 Γ ± 0.0031 N=95 ^f	0.0962 ± 0.0041 N=53 ^g	0.0984 ± 0.0040 N=41	0.1044 δ ± 0.0044 N=49	0.0976 ± 0.0036 N=49 ^g	0.0957 ± 0.0044 N=38	0.0985 ± 0.0066 N=45	0.1159 $\delta\delta\delta$ ± 0.0061 N=32
Relative Uterus with Cervix and Vagina Weight (% sacrifice weight) ^C	0.4340 $\Gamma\Gamma\Gamma$ ± 0.0262 N=96	0.4620 ± 0.0273 N=54	0.5155 ± 0.0396 N=41	0.4418 ± 0.0326 N=49	0.4280 ± 0.0227 N=51	0.4581 ± 0.0354 N=38	0.4874 ± 0.0414 N=45	1.8565 $\delta\delta\delta$ ± 0.1275 N=32

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 8 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% brain weight) ^c	15.5360 ± 0.4878 N=94 ^h	16.5904 ± 0.6422 N=53 ^f	16.7222 ± 0.8557 N=40 ^h	17.0837 ± 0.6936 N=48 ^h	16.1003 ± 0.6176 N=51	16.6673 ± 0.9320 N=37 ^h	14.2350 ± 1.0997 N=45	15.5546 ± 1.1865 N=32
Relative Liver Weight (% brain weight) ^c	123.7099 ± 2.9259 N=94 ^h	131.1232 ± 3.2119 N=54	127.2373 ± 3.5672 N=40 ^h	132.8262 ± 4.1363 N=48 ^h	125.1968 ± 3.9734 N=51	129.1216 ± 5.2687 N=37 ^h	111.4425 ± 5.7214 N=45	129.9728 ± 4.2203 N=32
Relative Spleen Weight (% brain weight) ^c	17.7928 Γ ± 0.6588 N=94 ^h	16.9923 ± 0.8596 N=54	16.5309 ± 0.8825 N=40 ^h	17.2339 ± 1.0149 N=48 ^h	17.6415 ± 0.9314 N=51	17.3343 ± 1.4646 N=37 ^h	12.2997 $\delta\delta\delta$ ± 1.2774 N=45	16.0725 ± 0.9338 N=32
Relative Right Kidney Weight (% brain weight) ^c	21.4317 ± 0.4459 N=94 ^h	22.1948 ± 0.5346 N=53 ^f	21.8438 ± 0.7239 N=40 ^h	23.1874 ± 0.8820 N=48 ^h	22.0376 ± 0.7658 N=51	22.9754 ± 0.8736 N=37 ^h	20.7354 ± 1.1061 N=45	22.7752 ± 0.8683 N=32
Relative Left Kidney Weight (% brain weight) ^c	20.6706 ± 0.4079 N=94 ^h	21.5866 ± 0.5417 N=53 ^f	20.9428 ± 0.6615 N=40 ^h	22.3675 ± 0.8144 N=48 ^h	21.4197 ± 0.7312 N=51	22.2787 ± 0.9114 N=37 ^h	20.2420 ± 1.0694 N=45	22.0063 ± 0.7669 N=32
Relative Paired Ovary Weight (% brain weight) ^c	2.0719 $\Gamma\Gamma\Gamma$ ± 0.0654 N=93 ^{f,h}	2.3201 δ ± 0.1017 N=53 ^g	2.2938 ± 0.1060 N=40 ^h	2.5562 $\delta\delta\delta$ ± 0.1174 N=48 ^h	2.3258 δ ± 0.1018 N=49 ^g	2.2531 ± 0.1084 N=37 ^h	1.9825 ± 0.1230 N=45	2.8969 $\delta\delta\delta$ ± 0.1696 N=32
Relative Uterus with Cervix and Vagina Weight (% brain weight) ^c	10.1676 $\Gamma\Gamma\Gamma$ ± 0.6155 N=94 ^h	11.2226 ± 0.6984 N=54	12.4356 ± 0.9801 N=40 ^h	10.9295 ± 0.8848 N=48 ^h	10.3091 ± 0.7034 N=51	10.8477 ± 0.8308 N=37 ^h	9.7956 ± 0.7826 N=45	46.6513 $\delta\delta\delta$ ± 3.6102 N=32

Table 22. Summary and Statistical Analysis of the F₁ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 9 of 9)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups.
- ^bAll pups had a macroscopic necropsy examination with sacrifice weight recorded and anogenital distance measured. A maximum of two pups per sex per litter also had specified organ weights recorded
- ^cReported as the mean \pm S.E.M. (adjusted for intralitter correlation).
- ^dDecrease in N is due to one sacrifice weight inadvertently not being recorded
- ^eReported as the mean \pm S E M. (adjusted for intralitter correlation and sacrifice weight as covariate).
- ^fDecrease in N is due to one or more weights being statistical outliers and, therefore, they were excluded.
- ^gDecrease in N is due to all or part of the organ/tissue from one or more animals being lost at necropsy prior to weighing.
- ^hDecrease in N is due to one or more brain weights being excluded because they were statistical outliers.
- ⁱThe necropsy sheet for dam 16, pup 3 was lost after the macroscopic necropsy had been done, therefore data were available for only 100 pups
- ^Γ $p < 0.05$, Wald Chi-square Test for overall treatment effect for correlated data.
- ^Π $p < 0.01$; Wald Chi-square Test for overall treatment effect for correlated data.
- ^{ΠΠ} $p < 0.001$; Wald Chi-square Test for overall treatment effect for correlated data
- ^δ $p < 0.05$; Individual t-test for pairwise comparison to control for correlated data.
- ^{δδ} $p < 0.01$, Individual t-test for pairwise comparison to control for correlated data
- ^{δδδ} $p < 0.001$; Individual t-test for pairwise comparison to control for correlated data.
- ^{ΓΓΓ} $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model with correlated data and sacrifice weight as a covariate.
- ^θ $p < 0.05$, Individual t-test for pairwise comparisons to control in robust regression model with correlated data and sacrifice weight as a covariate
- ^{θθ} $p < 0.01$; Individual t-test for pairwise comparisons to control in robust regression model with correlated data and sacrifice weight as a covariate.
- ^{θθθ} $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model with correlated data and sacrifice weight as a covariate

Table 23 Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 1 of 6)

MACROSCOPIC FINDINGS

Sex ^a	Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
		0 ^b	0.018	0.18	1.8	30	300	3500	0.5
F	Adrenal Gland: enlarged, right	1							
	Anal Opening: dried blood present						1		
	Brain: cerebral hemisphere longer than normal, left						1		
	Cervix: enlarged		1				2	1	
	Eye: opaque and sunken, left					1			
	Kidney: agenesis, right	1							
	Liver: pale			2		1			
	Ovary: cyst, left	1	1		1			1	
	cyst, right		1		1				
	fluid filled cyst, left	1							
	red, left				1				
	red, right		1						
	Spleen: enlarged							1	
	Tail: half missing	1							
	necrotic, tip	1							
	Thymus: reduced in size							1	
	Urinary Bladder: pitted and thickened					1			
	Uterus: fluid filled, bilateral								45
	fluid filled, left horn								1
	red, right horn		1						
Vagina: enlarged		1					1	2	
enlarged and open							1	22	
enlarged and thickened								2	
enlarged, open and thickened								3	
open		1						5	
M	Abdominal Mesentery: 3 mm diameter clear fluid filled cyst								1
	Epididymis: enlarged, right cauda					1			
	red, right			1					
	Kidney: hydronephrosis, right							2	2
round and small, right						1			

Table 23 Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 2 of 6)

MACROSCOPIC FINDINGS

Sex ^a	Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
		0 ^b	0.018	0.18	1.8	30	300	3500	0.5
M	Liver 3 x 3 mm darkened area, median lobe pale				1				
	Tail, kinked, tip necrotic, tip								2
	Testis: red, bilateral			1					1
	red, left			1				1	
	red, right		1	1	1		2		
	undescended								3
	undescended, bilateral	8	2	3	8	4	4	9	24
	undescended, left	2		1	1		3	1	
	undescended, right	1	3	1	1	1		2	
	Thoracic Cavity: full of congealed blood	1							

135 79 54 70 78 68 56 53

MICROSCOPIC FINDINGS FOR THE FEMALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
ADRENAL GLAND^c								
Number Examined	1							
No Findings								
BRAIN								
Number Examined	46	27	20	24	25	18	23	14
No Findings								
CERVIX								
Number Examined	89 ^d	51 ^d	30 ^d	42 ^d	43 ^d	31 ^d	38 ^d	29 ^d
No Findings								

Table 23 Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 3 of 6)

MICROSCOPIC FINDINGS FOR THE FEMALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>EYE^C</u>								
Number Examined					1			
No Findings								
<u>KIDNEY</u>								
Number Examined	46	27	20	24	25	18	22	14
Cyst, Cortex	2			1	1			
Cyst, Medulla		1	1					
Mineralization, Vein	1							
Regeneration, Renal Tubule	6	5	2	3	2	2	3	5
<u>LIVER</u>								
Number Examined	46	27	21	24	26	18	22	14
Cytoplasmic Alteration, Hepatocyte, Centriobular	2	1	2	3	4	6	6	1
Infiltrative Cell, Mononuclear Cell	1	1						
<u>OVARY</u>								
Number Examined	96	54	40 ^d	49	50 ^d	38	45	32
Cyst, Bursal	1			1				
Cyst, Parovarian	2	3		1		1	1	2
<u>SPLEEN</u>								
Number Examined	46	26 ^d	20	24	25	18	23	14
No Findings								
<u>TAIL^C</u>								
Number Examined	2							
Necrosis	1							

Table 23. Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 4 of 6)

MICROSCOPIC FINDINGS FOR THE FEMALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>THYMUS</u>								
Number Examined	43 ^d	26 ^d	19 ^d	22 ^d	24 ^d	15 ^d	22	14
Atrophy							1	
<u>URINARY BLADDER^C</u>								
Number Examined					1			
Inflammation, Chronic					1			
<u>UTERINE HORN</u>								
Number Examined	96	54	41	49	50 ^d	38	45	47
Dilatation, Lumen, Bilateral								45
<u>VAGINA</u>								
Number Examined	93 ^d	53 ^d	41	46 ^d	49 ^d	38	44 ^d	37
Epithelium, Keratinized	8	7	3	4	2	2	5	34

MICROSCOPIC FINDINGS FOR THE MALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>ABDOMINAL MESENTERY</u>								
Number Examined								0 ^d
<u>BRAIN</u>								
Number Examined	44	26	17	21	24	20	20	16
No Findings								

Table 23 Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 5 of 6)

MICROSCOPIC FINDINGS FOR THE MALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
COAGULATING GLAND								
Number Examined	67 ^d	48 ^d	30 ^d	34 ^d	38 ^d	35 ^d	29 ^d	23 ^d
No Findings								
EPIDIDYMIS								
Number Examined	92	53	37	44	51	42	42	34
No Findings								
KIDNEY								
Number Examined	44	26	17	21	24	21	21	18
Cyst, Cortex						1	1	1
Cyst, Medulla					1			
Hydronephrosis, Unilateral							3	2
Mineralization, Corticomedullary Junction								1
Regeneration, Renal Tubule	6	2	2	2	4	1	3	3
LIVER								
Number Examined	44	26	17	22	24	20	20	17
Cytoplasmic Alteration, Hepatocyte, Centrilobular	6	1		1	6	10	13	2
Hemorrhage				1				
Infiltrative Cell, Mononuclear Cell			1		1			
Vacuolar Degeneration, Hepatocyte, Centrilobular	1							
SEMINAL VESICLE								
Number Examined	84 ^d	50 ^d	35 ^d	42 ^d	47 ^d	38 ^d	35 ^d	29 ^d
No Findings								
SPLEEN								
Number Examined	44	25 ^d	17	21	24	20	20	16
No Findings								

Table 23 Summary of the F₁ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 6 of 6)

MICROSCOPIC FINDINGS FOR THE MALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>TAIL^c</u>								
Number Examined			1					1
Necrosis			1					
<u>TESTIS</u>								
Number Examined	96	54	37	45	51	45	43	43
Atrophy, Seminiferous Tubule, Unilateral	1				1	1		
Dilatation, Rete Testis	2			1		1		
Dilatation, Seminiferous Tubule, Bilateral		1						
Dilatation, Seminiferous Tubule, Unilateral	2	1					3	
Hypoplasia, Seminiferous Tubule	1			1	3	2	5	10
<u>THYMUS</u>								
Number Examined	41 ^d	25 ^d	16 ^d	18 ^d	23 ^d	19 ^d	19 ^d	16
No Findings								

^aF is female and M is male.

^bCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^cIncludes only those pups with a macroscopic necropsy finding for this tissue.

^dThere was not a section of this tissue available for evaluation for one or more pups.

Table 24. Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 1 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
No of F ₀ Females at Scheduled Sacrifice	56	28	27 ^b	27 ^c	27 ^d	28	28	28
Sacrifice Body Weight (g) ^e	34.87 ± 0.38 N=56	35.36 ± 0.60 N=28	35.34 ± 0.59 N=27	35.33 ± 0.54 N=27	34.71 ± 0.42 N=27	34.47 ± 0.50 N=28	35.68 ± 0.68 N=28	33.26 ± 0.64 N=28
Brain Weight (g) ^e #	0.5304 ± 0.0051 N=56	0.5282 ± 0.0057 N=28	0.5307 ± 0.0074 N=27	0.5367 ± 0.0061 N=27	0.5417 ± 0.0060 N=27	0.5389 ± 0.0066 N=28	0.5443 ± 0.0097 N=28	0.5420 ± 0.0070 N=28
Pituitary Weight (g) ^e	0.0038 ± 0.0001 N=56	0.0037 ± 0.0001 N=27 ^f	0.0037 ± 0.0001 N=27	0.0036 ± 0.0001 N=26 ^g	0.0038 ± 0.0001 N=27	0.0035 ± 0.0001 N=27 ^f	0.0038 ± 0.0001 N=28	0.0039 ± 0.0001 N=27 ^f
Thyroid Weight (g) ^e	0.0030 ± 0.0001 N=54 ^{f,g}	0.0032 ± 0.0001 N=28	0.0032 ± 0.0001 N=26 ^f	0.0033 ± 0.0001 N=27	0.0033 ± 0.0001 N=27	0.0030 ± 0.0001 N=26 ^f	0.0031 ± 0.0001 N=28	0.0032 ± 0.0001 N=27 ^f
Liver Weight (g) ^e #	2.7327 ††† ± 0.0642 N=56	2.8711 ± 0.0852 N=28	2.7517 ± 0.0982 N=27	2.7848 ± 0.0811 N=27	2.6030 ± 0.0520 N=27	2.7099 ± 0.0879 N=28	3.2928 ††† ± 0.1515 N=28	2.4347 † ± 0.0987 N=28
Spleen Weight (g) ^e	0.1373 ± 0.0043 N=55 ^h	0.1393 ± 0.0065 N=28	0.1470 ± 0.0084 N=27	0.1465 ± 0.0068 N=27	0.1414 ± 0.0064 N=27	0.1694 ± 0.0205 N=28	0.1440 ± 0.0089 N=28	0.1475 ± 0.0094 N=28
Right Kidney Weight (g) ^e	0.3083 †† ± 0.0063 N=56	0.3162 ± 0.0092 N=28	0.3218 ± 0.0076 N=27	0.3223 ± 0.0067 N=27	0.3263 ± 0.0058 N=27	0.3239 ± 0.0080 N=28	0.3535 *** ± 0.0082 N=28	0.3092 ± 0.0084 N=28

Table 24 Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Relative Liver Weight (% sacrifice weight) ^e								
#	7 8075 †††	8.0881	7.7499	7.8570	7 4910	7 8368	9 1619 †††	7.2644 †
	± 0.1417	± 0.1552	± 0.1990	± 0.1578	± 0.0977	± 0.1987	± 0.3222	± 0.1904
	N=56	N=28	N=27	N=27	N=27	N=28	N=28	N=28
Relative Spleen Weight (% sacrifice weight) ^e								
	0.3960	0.3935	0.4164	0.4152	0.4118	0.4985	0.4068	0.4473
	± 0.0130	± 0.0160	± 0.0232	± 0.0183	± 0.0224	± 0.0667	± 0.0265	± 0.0301
	N=55 ^h	N=28	N=27	N=27	N=27	N=28	N=28	N=28
Relative Right Kidney Weight (% sacrifice weight) ^e								
	0.8844 ††	0.8924	0.9124	0.9134	0.9425	0.9441	0.9952 ***	0.9291
	± 0.0158	± 0.0194	± 0.0191	± 0.0153	± 0.0180	± 0.0263	± 0.0220	± 0.0186
	N=56	N=28	N=27	N=27	N=27	N=28	N=28	N=28
Relative Left Kidney Weight (% sacrifice weight) ^e								
	0.8781 ††	0.8606	0.9030	0.8955	0.9235	0.9272	0.9746 **	0.9071
	± 0.0158	± 0.0183	± 0.0237	± 0.0153	± 0.0151	± 0.0280	± 0.0244	± 0.0195
	N=56	N=27 ^g	N=27	N=27	N=27	N=28	N=28	N=28
Relative Paired Adrenal Gland Weight (% sacrifice weight) ^e								
	0.0383	0.0351	0.0366	0.0397	0.0369	0.0421	0.0378	0.0398
	± 0.0016	± 0.0017	± 0.0023	± 0.0019	± 0.0020	± 0.0029	± 0.0016	± 0.0020
	N=56	N=27 ^g	N=26 ^g	N=27	N=26 ^g	N=28	N=28	N=28
Relative Paired Ovary Weight (% sacrifice weight) ^e								
	0.1123	0.1088	0.1084	0.1211	0.1162	0.1175	0.1080	0.1211
	± 0.0040	± 0.0054	± 0.0039	± 0.0047	± 0.0059	± 0.0050	± 0.0052	± 0.0070
	N=56	N=28	N=27	N=27	N=27	N=28	N=28	N=28
Relative Uterus with Cervix and Vagina Weight (% sacrifice weight) ^e								
	0.8789 †††	0.9427	0.9524	0.9104	0.9474	0.9818	0.8858	1.2480 ***
	± 0.0408	± 0.0489	± 0.0507	± 0.0563	± 0.0708	± 0.0725	± 0.0582	± 0.0684
	N=56	N=28	N=27	N=27	N=27	N=28	N=28	N=28

Table 24 Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Relative Pituitary Weight (% brain weight) ^e	0.7197 ± 0.0152 N=56	0.7089 ± 0.0240 N=27 ^f	0.6955 ± 0.0231 N=27	0.6749 ± 0.0183 N=26 ^g	0.7023 ± 0.0198 N=27	0.6418 ± 0.0241 N=27 ^f	0.7122 ± 0.0254 N=28	0.7207 ± 0.0226 N=27 ^f
Relative Thyroid Weight (% brain weight) ^e	0.5691 ± 0.0148 N=54 ^{f,g}	0.6099 ± 0.0227 N=28	0.6042 ± 0.0260 N=26 ^f	0.6212 ± 0.0220 N=27	0.6037 ± 0.0177 N=27	0.5561 ± 0.0200 N=26 ^f	0.5796 ± 0.0217 N=28	0.6009 ± 0.0242 N=27 ^f
Relative Liver Weight (% brain weight) ^e #	518.9309 ††† ± 13.8889 N=56	545.0273 ± 16.3616 N=28	522.1198 ± 20.7190 N=27	519.5298 ± 14.4475 N=27	480.9566 † ± 9.0003 N=27	504.8822 ± 17.4247 N=28	614.5013 ††† ± 33.2187 N=28	450.9496 †† ± 18.7250 N=28
Relative Spleen Weight (% brain weight) ^e	25.9053 ± 0.7754 N=55 ^h	26.2941 ± 1.1036 N=28	27.7150 ± 1.4645 N=27	27.2997 ± 1.1748 N=27	26.2049 ± 1.2493 N=27	31.9608 ± 4.4236 N=28	26.5948 ± 1.7917 N=28	26.9927 ± 1.5240 N=28
Relative Right Kidney Weight (% brain weight) ^e	58.3821 ‡ ± 1.3101 N=56	60.0316 ± 1.7632 N=28	60.9265 ± 1.6438 N=27	60.2024 ± 1.3226 N=27	60.3565 ± 1.1323 N=27	60.1942 ± 1.4408 N=28	65.4950 ** ± 1.8498 N=28	57.2861 ± 1.6662 N=28
Relative Left Kidney Weight (% brain weight) ^e	57.9333 ‡ ± 1.2631 N=56	57.8504 ± 1.4404 N=27 ^g	60.2322 ± 1.7254 N=27	59.0162 ± 1.2814 N=27	59.1552 ± 0.9864 N=27	58.9990 ± 1.4046 N=28	64.1210 * ± 1.9182 N=28	55.8974 ± 1.7016 N=28
Relative Paired Adrenal Gland Weight (% brain weight) ^e	2.5017 ± 0.0982 N=56	2.3197 ± 0.0952 N=27 ^g	2.4251 ± 0.1306 N=26 ^g	2.5987 ± 0.1117 N=27	2.3493 ± 0.1107 N=26 ^g	2.6461 ± 0.1555 N=28	2.4646 ± 0.0908 N=28	2.4222 ± 0.1145 N=28

Table 24. Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Paired Ovary Weight (% brain weight) ^e	7.3729 ± 0.2555 N=56	7.2427 ± 0.3325 N=28	7.1889 ± 0.2283 N=27	7.9836 ± 0.3288 N=27	7.4244 ± 0.3628 N=27	7.5151 ± 0.3344 N=28	7.0528 ± 0.3363 N=28	7.3572 ± 0.3913 N=28
Relative Uterus with Cervix and Vagina Weight (% brain weight) ^e	57.5772 †† ± 2.5797 N=56	63.1716 ± 3.5091 N=28	62.9782 ± 3.0756 N=27	59.6553 ± 3.6085 N=27	60.3262 ± 4.3084 N=27	61.9434 ± 4.1559 N=28	57.1511 ± 2.9720 N=28	76.0253 *** ± 3.7094 N=28
Paired Ovarian Follicle Counts ^{e, l}	92.1 ± 5.0 N=56						92.0 ± 7.0 N=28	95.0 ± 5.5 N=28

Table 24 Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 6 of 7)

	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>VAGINAL CYTOLOGY EVALUATION AT NECROPSY</u> ^j								
No. of F ₀ Females Evaluated	56	28	27 ^b	27 ^c	27 ^d	28	28	28
Number in Proestrus	0	0	0	0	0	0	0	0
Percent in Proestrus	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Number in Estrus	10	9	6	10	8	9	9	10
Percent in Estrus	17.86	32.14	22.22	37.04	29.63	32.14	32.14	35.71
Number in Metestrus	7	4	3	0	1	2	2	11
Percent in Metestrus	12.50 £££	14.29	11.11	0.00	3.70	7.14	7.14	39.29 Φ
Number in Diestrus	39	15	18	17	18	17	17	7
Percent in Diestrus	69.64 £	53.57	66.67	62.96	66.67	60.71	60.71	25.00 $\Phi\Phi\Phi$
Number Stage Not Determined	0	0	0	0	0	0	0	0
Number No Cells Present ^k	0	0	0	0	0	0	0	0

Table 24. Summary and Statistical Analysis of the F₀ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 7 of 7)

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups

^bFemale 368 found dead on postnatal day 11 (study day 90).

^cFemale 14 was found dead on postnatal day 14 (study day 95)

^dFemale 22 was found dead on study day 87.

^eReported as the mean \pm S.E.M..

^fDecrease in N is due to part or all of one or more organs not being present in the tissue cup at the time of weighing the fixed organ

^gDecrease in N is due to one weight being a statistical outlier and, therefore, it was excluded

^hDecrease in N is due to part of the spleen not being present at the time of weighing, therefore the spleen weight was not recorded

ⁱOvarian follicle counts were done for all control females, all females in the 3500 ppm dose group and all females in the 0.5 ppm 17 β -Estradiol dose group.

^jFor presentation and statistical analysis purposes those females in two stages were pooled in the following manner: proestrus/estrus and estrus/proestrus were considered proestrus; estrus/metestrus and metestrus/estrus were considered estrus; metestrus/diestrus and diestrus/metestrus were considered metestrus; and diestrus/proestrus and proestrus/diestrus were considered diestrus. The females for which the stage could not be determined or no cells were present were not included in the statistical analysis

^kThese smears did not contain sloughed cells or the cells washed off during processing and, therefore, they could not be evaluated

[#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects

[†] $p < 0.05$; ANOVA Test.

^{††} $p < 0.01$; ANOVA Test

^{†††} $p < 0.001$; ANOVA Test.

^{*} $p < 0.05$; Dunnett's Test.

^{**} $p < 0.01$; Dunnett's Test.

^{***} $p < 0.001$; Dunnett's Test.

^{†††} $p < 0.001$, Wald Chi-square Test for overall treatment effect in robust regression model.

[†] $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model.

^{††} $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model.

^{†††} $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model.

[£] $p < 0.05$; Chi-Square Test.

^{£££} $p < 0.001$; Chi-Square Test.

^Φ $p < 0.05$, Fishers' Exact Test.

^{ΦΦΦ} $p < 0.001$; Fishers' Exact Test.

Table 25. Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 1 of 6)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Alopecia, multiple areas	1							
nose		1						
Cerebellum: irregular shape						1		
Cervix: thickened								4
Gall Bladder: enlarged and fluid filled			1					
thickened and protruding from liver						1		
Intestines: filled with air							1	
Kidney: enlarged, bilateral	1							
reduced in size, right	1	1						
Lymph Nodes, Cervical and Mammary: enlarged, bilateral						1		
Mammary Glands, Axillary: enlarged						1		
Nipple(s): discolored, brown/greenish, two								1
Ovary, cyst(s), bilateral	2			1	1	1		1
cyst(s), clear, bilateral							1	
cyst(s), clear, left							1	
cyst(s), dark brown fluid, left					1			
cyst(s), fluid filled, left	1	1						2
cyst(s), left	3		2	3		1	1	1
cyst(s), red fluid filled, right		1						
cyst(s), right	1	3	2		2	1	6	2
encapsulated cyst(s), right								1
encapsulated dark green mass, left				1				
reddened and fluid filled, left	1							
Salivary Glands: enlarged, bilateral						1		
Sore(s): neck and axillary mammary gland area						1		
Spleen: enlarged						1	1	1
Tail: 2.4 mm of distal end dried and brown					1			

Table 25 Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 2 of 6)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Uterus: early resorption					1			
early resorption, left horn	1		1					
early resorption, right horn				1		1		1
enlarged				1				
enlarged and thickened		1			1			
enlarged and thickened, bilateral					1			1
fluid filled		1				1		
fluid filled, bilateral	4	1	1		1	4	1	1
implant sites very light in color								1
resorption, at cervix		1						
resorption, right horn		1						
thickened								1
thickened and implant sites very light in color								1
thickened, bilateral							1	2
Vagina: enlarged								2
thickened								4

UNSCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Kidney: multiple tan nodules on surface and into cortex upper pole, left					1			
Kidney: reduced in size and two tan nodules on surface extending into renal pelvis, right					1			
Tissue too autolyzed to evaluate			1	1				

Table 25. Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 3 of 6)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>Adrenal Gland</u>								
Number Examined	56	10	10	10	10	10	10	10
Hyperplasia, Spindle Cell	24	4	5	3	4	5	3	6
Regression, X-zone						1		
<u>Brain^b</u>								
Number Examined						1		
No Findings								
<u>Cervix^c</u>								
Number Examined	55 ^d	11	12	11	12	14	12 ^d	15 ^d
No Findings								
<u>Gallbladder^b</u>								
Number Examined						1		
No Findings								
<u>Intestine - Large, Colon^b</u>								
Number Examined							1	
Inflammation, Subacute							1	

Table 25. Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 4 of 6)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Kidney								
Number Examined	56	10	10	10	11	10	10	10
Cyst, Cortex	5		1		1	1		1
Hypertrophy, Renal Tubule		1						
Infiltrative Cell, Mononuclear Cell	10	2	2	1	2		1	3
Inflammation, Chronic						1	1	
Inflammation, Tubulointerstitial, Medulla	7	2	2			1	1	3
Mineralization, Corticomedullary Junction	1							
Mineralization, Papillae	3		1				1	2
Nephropathy	10	3		2	1	3	2	2
Polycystic Kidney, Bilateral							1	
Pyelonephritis, Bilateral, Acute					1			
Liver								
Number Examined	56	10	10	10	10	10	10	10
Cyst, Bile Duct								1
Hypertrophy, Hepatocyte, Centrilobular	1					1	6	
Infiltrative Cell, Mononuclear Cell	4		2		1	1		1
Necrosis, Hepatocyte, Focal	3	1		2		3	2	
Polycystic, Bile Duct	1							
Lymph Node, Cervical^b								
Number Examined						1		
Infiltrative Cell, Plasma Cell						1		
Lymph Node, Mammary^b								
Number Examined						1		
Infiltrative Cell, Plasma Cell						1		

Table 25 Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 5 of 6)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Mammary								
Number Examined	55 ^d	10	10	10	10	11	10	9 ^d
Abscess, Lymph Node, Mammary					1			
Inflammation, Dermis, Subacute		1						
Inflammation, Subacute	3	1				2		
Ulcer, Epithelium, Skin								1
Ovary^c								
Number Examined	56	11	12	11	12	14	17	20
Atrophy		1						
Cyst, Bursal	2	1		1	1	1		
Cyst, Follicle	2							
Cyst, Paraovarian	9	1	2	1	1	3	7	10
Pituitary								
Number Examined	56	10	10	10	10	10	10	10
No Findings								
Salivary Gland^b								
Number Examined						1		
No Findings								
Skin^b								
Number Examined	1					1		
Ulcer, Epithelium						1		
Skin, Back^b								
Number Examined			1					
No Findings								

Table 25 Summary of the F₀ Female Macroscopic and Microscopic Necropsy Findings (page 6 of 6)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>Spleen</u>								
Number Examined	56	10	10	10	10	11	11	10
Hematopoietic Cell Proliferation	2	1	1	2	2	4	2	2
Hyperplasia, Lymphoid	1							
<u>Thyroid</u>								
Number Examined	56	10	10	10	10	10	10	10
Cyst, Follicle	2					1		1
Ectopic Thymus	2		1	1				2
Infiltrative Cell, Mononuclear Cell					1			
<u>Uterine Horn^c</u>								
Number Examined	56	11	12	11	12	14	13	18
Cyst, Endometrium			1			1	2	4
Decidual Reaction	1							
Mineralization, Broad Ligament	1							
Necrotic Debris, Lumen		1						
<u>Vagina^c</u>								
Number Examined	56	11	12	11	12	14	13	18
Inflammation, Acute (Total)						1		
minimal						1		

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^bIncludes only those females with a macroscopic necropsy finding for this tissue.

^cIncludes females with suspected reduced fertility.

^dThere was not a section of this tissue available for evaluation for one or more females.

Table 27. Summary and Statistical Analysis of the F₁ Parental Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. of F ₁ Parental Males Evaluated	56	28	27 ^b	28	28	28	27 ^c	28
Day of Preputial Separation ^d #	26.0 ††† ± 0.2 N=56	26.0 ± 0.3 N=28	26.1 ± 0.4 N=27	25.9 ± 0.3 N=28	25.9 ± 0.4 N=28	26.3 ± 0.4 N=28	27.9 bb ± 0.6 N=27	32.8 ddd ± 0.7 N=28
Body Weight (g) on Day of Acquisition ^d	18.31 ††† ± 0.27 N=56	18.64 ± 0.41 N=28	18.69 ± 0.45 N=27	18.42 ± 0.36 N=28	17.54 ± 0.31 N=28	18.54 ± 0.36 N=28	17.65 ± 0.40 N=27	22.25 *** ± 0.43 N=28
Adjusted Day of Preputial Separation ^e	26.2 ††† ± 0.2 N=56	26.1 ± 0.3 N=28	26.2 ± 0.4 N=27	26.0 ± 0.3 N=28	26.3 ± 0.4 N=28	26.3 ± 0.4 N=28	28.2 ooo ± 0.5 N=27	31.6 ooo ± 0.7 N=28
Body Weight (g) on Postnatal Day 30 ^d	23.73 ††† ± 0.35 N=56	24.06 ± 0.47 N=28	24.32 ± 0.64 N=27	24.29 ± 0.48 N=28	23.34 ± 0.70 N=28	23.67 ± 0.59 N=28	20.47 *** ± 0.73 N=26 ^f	20.06 *** ± 0.47 N=28
Adjusted Day of Preputial Separation ^g	26.4 ††† ± 0.2 N=56	26.6 ± 0.2 N=28	26.8 ± 0.3 N=27	26.5 ± 0.2 N=28	26.1 ± 0.2 N=28	26.6 ± 0.2 N=28	26.5 ± 0.4 N=27	31.2 ooo ± 0.6 N=28

Table 27. Summary and Statistical Analysis of the F₁ Parental Male Preputial Separation Data (page 2 of 2)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups
- ^bMale 1275 was found dead on study day -13, which was postnatal day 23 (negative study days were during the postwean holding period prior to the start of the prebreed period)
- ^cMale 1201 was euthanized moribund on study day -10, which was postnatal day 23 (negative study days were during the postwean holding period prior to the start of the prebreed period).
- ^dReported as the mean \pm S.E.M with day being postnatal day.
- ^eReported as the adjusted mean (body weight at acquisition as covariate) \pm S.E.M
- ^fDecrease in N is due to one body weight inadvertently not being recorded on postnatal day 30.
- ^gReported as the adjusted mean (body weight on postnatal day 30 as covariate) \pm S.E.M
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.
- ^{†††} $p < 0.001$, Wald Chi-square Test for overall treatment effect in robust regression model
- ^{bb} $p < 0.01$; Individual t-test for pairwise comparisons to control in robust regression model.
- ^{bbb} $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model.
- ^{†††} $p < 0.001$; ANOVA Test
- ^{***} $p < 0.001$, Dunnett's Test.
- ^{ΣΣΣ} $p < 0.001$, Wald Chi-square Test for overall treatment effect in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate
- ^{σσσ} $p < 0.001$, Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate.

Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 1 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. of F ₁ Parental Males at Scheduled Sacrifice	55 ^b	28	27 ^c	28	28	28	27 ^d	28
Sacrifice Body Weight (g) ^e	38.89 ± ± 0.53 N=54 ^f	40.03 ± ± 0.81 N=27 ^f	39.85 ± ± 0.72 N=27	39.51 ± ± 0.66 N=28	38.61 ± ± 0.64 N=28	38.64 ± ± 0.76 N=27 ^g	37.44 ± ± 0.55 N=27	37.06 ± ± 0.57 N=28
Brain Weight (g) ^e	0.5151 ± ± 0.0037 N=55	0.5184 ± ± 0.0056 N=28	0.5161 ± ± 0.0056 N=26 ^h	0.5297 ± ± 0.0050 N=28	0.5168 ± ± 0.0061 N=28	0.5272 ± ± 0.0054 N=28	0.5145 ± ± 0.0066 N=26 ^h	0.5190 ± ± 0.0058 N=27 ^h
Pituitary Weight (g) ^e	0.0026 †† ± 0.0001 N=53 ^{i,j}	0.0026 ± ± 0.0001 N=24 ^j	0.0025 ± ± 0.0001 N=27	0.0026 ± ± 0.0001 N=28	0.0027 ± ± 0.0001 N=25 ^j	0.0025 ± ± 0.0001 N=28	0.0028 ± ± 0.0001 N=26 ^j	0.0029 * ± 0.0001 N=28
Thyroid Weight (g) ^e	0.0026 ± ± 0.0001 N=54 ^j	0.0026 ± ± 0.0001 N=25 ^j	0.0026 ± ± 0.0001 N=25 ^j	0.0027 ± ± 0.0001 N=28	0.0025 ± ± 0.0001 N=27 ^j	0.0025 ± ± 0.0001 N=28	0.0027 ± ± 0.0001 N=26 ^j	0.0028 ± ± 0.0001 N=27 ^j
Liver Weight (g) ^e	2.0738 ††† ± 0.0390 N=55	2.1207 ± ± 0.0386 N=28	2.0875 ± ± 0.0435 N=27	2.1581 ± ± 0.0483 N=28	2.1052 ± ± 0.0467 N=28	2.1385 ± ± 0.0512 N=28	2.4282 *** ± 0.0864 N=27	2.0701 ± ± 0.0512 N=28
Spleen Weight (g) ^e	0.1080 ± ± 0.0033 N=55	0.1110 ± ± 0.0043 N=27 ^f	0.1048 ± ± 0.0037 N=27	0.1055 ± ± 0.0048 N=28	0.1084 ± ± 0.0043 N=28	0.1100 ± ± 0.0066 N=28	0.1043 ± ± 0.0044 N=27	0.1043 ± ± 0.0036 N=28
Right Kidney Weight (g) ^e #	0.3732 ††† ± 0.0065 N=55	0.3975 ± ± 0.0137 N=28	0.3895 ± ± 0.0106 N=27	0.4006 †† ± 0.0074 N=28	0.4119 †† ± 0.0111 N=28	0.4053 †† ± 0.0104 N=28	0.4378 ††† ± 0.0133 N=27	0.4000 †† ± 0.0072 N=28

Table 31 Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 2 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Left Kidney Weight (g) ^e #	0.3611 ††† ± 0.0071 N=55	0.3930 † ± 0.0128 N=28	0.3752 ± 0.0083 N=27	0.3850 † ± 0.0062 N=28	0.4042 ††† ± 0.0105 N=28	0.3926 † ± 0.0106 N=28	0.4252 ††† ± 0.0103 N=27	0.3880 †† ± 0.0059 N=28
Paired Adrenal Gland Weight (g) ^e	0.0069 ± 0.0002 N=53 [†]	0.0079 ± 0.0005 N=28	0.0067 ± 0.0004 N=26 [†]	0.0070 ± 0.0004 N=25 ^{†,k}	0.0069 ± 0.0004 N=26 [†]	0.0070 ± 0.0004 N=27 [†]	0.0070 ± 0.0004 N=26 [†]	0.0074 ± 0.0004 N=27 [†]
Paired Testis Weight (g) ^e	0.2623 ± 0.0045 N=55	0.2625 ± 0.0078 N=28	0.2651 ± 0.0057 N=27	0.2597 ± 0.0062 N=28	0.2684 ± 0.0072 N=28	0.2649 ± 0.0087 N=28	0.2482 ± 0.0058 N=27	0.2554 ± 0.0066 N=27 [†]
Paired Epididymis Weight (g) ^e	0.1111 ‡ ± 0.0018 N=55	0.1128 ± 0.0022 N=28	0.1080 ± 0.0024 N=27	0.1109 ± 0.0023 N=28	0.1117 ± 0.0022 N=27 [†]	0.1107 ± 0.0027 N=28	0.1033 * ± 0.0016 N=27	0.1063 ± 0.0021 N=28
Seminal Vesicles with Coagulating Gland Weight (g) ^e #	0.3415 †† ± 0.0075 N=55	0.3805 † ± 0.0143 N=28	0.3755 ± 0.0203 N=25 [†]	0.3542 ± 0.0097 N=28	0.3606 ± 0.0147 N=25 [†]	0.3772 † ± 0.0137 N=28	0.3262 ± 0.0084 N=26 [†]	0.3518 ± 0.0152 N=28
Ventral Prostate Weight (g) ^e	0.0265 ± 0.0014 N=55	0.0322 ± 0.0029 N=28	0.0301 ± 0.0030 N=26 [†]	0.0287 ± 0.0023 N=28	0.0309 ± 0.0026 N=28	0.0283 ± 0.0027 N=28	0.0253 ± 0.0021 N=26 [†]	0.0248 ± 0.0021 N=28
Dorsolateral Prostate Weight (g) ^e	0.0458 ± 0.0017 N=54 [†]	0.0474 ± 0.0024 N=27 [†]	0.0491 ± 0.0039 N=27	0.0505 ± 0.0036 N=28	0.0449 ± 0.0026 N=28	0.0437 ± 0.0027 N=28	0.0450 ± 0.0027 N=26 [†]	0.0422 ± 0.0030 N=28



Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 3 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Prostate Weight (g) ^e	0.0719 ± 0.0022 N=54 ^m	0.0801 ± 0.0040 N=27 ^m	0.0783 ± 0.0057 N=26 ^m	0.0792 ± 0.0045 N=28	0.0758 ± 0.0036 N=28	0.0720 ± 0.0040 N=28	0.0703 ± 0.0040 N=26 ^m	0.0671 ± 0.0041 N=28
Relative Brain Weight (% of sacrifice weight) ^e	1.3357 ‡ ± 0.0182 N=54 ⁿ	1.3048 ± 0.0198 N=27 ⁿ	1.2982 ± 0.0247 N=26 ⁿ	1.3492 ± 0.0226 N=28	1.3493 ± 0.0289 N=28	1.3825 ± 0.0310 N=27 ^g	1.3819 ± 0.0236 N=26 ^h	1.4085 ± 0.0210 N=27 ^h
Relative Pituitary Weight (% of sacrifice weight) ^e	0.0067 ††† ± 0.0001 N=52 ^{i,j,n}	0.0066 ± 0.0002 N=23 ^{i,n}	0.0063 ± 0.0002 N=27	0.0065 ± 0.0002 N=28	0.0070 ± 0.0002 N=25 ^j	0.0065 ± 0.0002 N=27 ^g	0.0074 * ± 0.0002 N=26 ^j	0.0077 *** ± 0.0002 N=28
Relative Thyroid Weight (% of sacrifice weight) ^e	0.0066 ‡ ± 0.0002 N=53 ^{l,n}	0.0066 ± 0.0003 N=24 ^{l,n}	0.0066 ± 0.0003 N=25 ⁱ	0.0069 ± 0.0003 N=28	0.0064 ± 0.0003 N=27 ⁱ	0.0065 ± 0.0003 N=27 ^g	0.0072 ± 0.0003 N=26 ^j	0.0076 * ± 0.0002 N=27 ^j
Relative Liver Weight (% of sacrifice weight) ^e #	5.3107 ††† ± 0.0588 N=54 ⁿ	5.2895 ± 0.0533 N=27 ⁿ	5.2486 ± 0.0837 N=27	5.4669 ± 0.0962 N=28	5.4497 ± 0.0709 N=28	5.5513 † ± 0.0744 N=27 ^g	6.4798 ††† ± 0.1995 N=27	5.5772 † ± 0.0876 N=28
Relative Spleen Weight (% of sacrifice weight) ^e	0.2770 ± 0.0077 N=54 ⁿ	0.2824 ± 0.0095 N=26 ^{f,n}	0.2646 ± 0.0099 N=27	0.2680 ± 0.0122 N=28	0.2826 ± 0.0116 N=28	0.2920 ± 0.0186 N=27 ^g	0.2794 ± 0.0116 N=27	0.2811 ± 0.0083 N=28
Relative Right Kidney Weight (% of sacrifice weight) ^e	0.9635 ††† ± 0.0142 N=54 ⁿ	0.9938 ± 0.0292 N=27 ⁿ	0.9800 ± 0.0238 N=27	1.0201 ± 0.0239 N=28	1.0677 ** ± 0.0240 N=28	1.0572 * ± 0.0202 N=27 ^g	1.1693 *** ± 0.0314 N=27	1.0852 *** ± 0.0246 N=28

Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 4 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Left Kidney Weight (% of sacrifice weight) ^e	0.9303 ††† ± 0.0155 N=54 ⁿ	0.9825 ± 0.0269 N=27 ⁿ	0.9455 ± 0.0203 N=27	0.9794 ± 0.0188 N=28	1.0478 *** ± 0.0233 N=28	1.0263 ** ± 0.0206 N=27 ^g	1.1358 *** ± 0.0224 N=27	1.0530 *** ± 0.0218 N=28
Relative Paired Adrenal Gland Weight (% of sacrifice weight) ^e	0.0178 ± 0.0007 N=52 ^{f,n}	0.0203 ± 0.0015 N=27 ⁿ	0.0169 ± 0.0010 N=26 ^f	0.0179 ± 0.0012 N=25 ^{f,k}	0.0180 ± 0.0009 N=26 ^f	0.0181 ± 0.0011 N=26 ^{f,g}	0.0187 ± 0.0011 N=26 ^f	0.0203 ± 0.0014 N=27 ^f
Relative Paired Testis Weight (% of sacrifice weight) ^e	0.6783 ± 0.0127 N=54 ⁿ	0.6608 ± 0.0193 N=27 ⁿ	0.6700 ± 0.0181 N=27	0.6587 ± 0.0141 N=28	0.7005 ± 0.0220 N=28	0.6985 ± 0.0225 N=27 ^g	0.6663 ± 0.0172 N=27	0.6983 ± 0.0215 N=27 ^f
Relative Paired Epididymis Weight (% of sacrifice weight) ^e	0.2867 ± 0.0044 N=54 ⁿ	0.2833 ± 0.0041 N=27 ⁿ	0.2723 ± 0.0062 N=27	0.2818 ± 0.0060 N=28	0.2894 ± 0.0062 N=27 ^f	0.2890 ± 0.0074 N=27 ^g	0.2770 ± 0.0051 N=27	0.2884 ± 0.0070 N=28
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight) ^e	0.8825 ± 0.0200 N=54 ⁿ	0.9551 ± 0.0374 N=27 ⁿ	0.9374 ± 0.0463 N=25 ^l	0.9063 ± 0.0321 N=28	0.9418 ± 0.0341 N=25 ^l	0.9774 ± 0.0326 N=27 ^g	0.8741 ± 0.0237 N=26 ^l	0.9517 ± 0.0415 N=28
Relative Ventral Prostate Weight (% of sacrifice weight) ^e	0.0685 ± 0.0037 N=54 ⁿ	0.0803 ± 0.0064 N=27 ⁿ	0.0757 ± 0.0073 N=26 ^f	0.0729 ± 0.0058 N=28	0.0806 ± 0.0069 N=28	0.0743 ± 0.0066 N=27 ^g	0.0670 ± 0.0054 N=26 ^f	0.0675 ± 0.0060 N=28
Relative Dorsolateral Prostate Weight (% of sacrifice weight) ^e	0.1183 ± 0.0044 N=53 ^{f,n}	0.1187 ± 0.0065 N=26 ^{f,n}	0.1230 ± 0.0091 N=27	0.1278 ± 0.0091 N=28	0.1165 ± 0.0067 N=28	0.1156 ± 0.0073 N=27 ^g	0.1198 ± 0.0071 N=26 ^f	0.1132 ± 0.0073 N=28

Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 5 of 8)

	Bisphenol A (ppm in the feed)						17β-Estradiol	
	0 ^a	0.018	0.18	1.8	30	300	(ppm in the feed)	
							0.5	
Relative Prostate Weight (% of sacrifice weight) ^e	0.1861 ± 0.0054 N=53 ^{m,n}	0.2004 ± 0.0088 N=26 ^{m,n}	0.1972 ± 0.0136 N=26 ^m	0.2008 ± 0.0111 N=28	0.1971 ± 0.0098 N=28	0.1899 ± 0.0097 N=27 ^g	0.1868 ± 0.0103 N=26 ^m	0.1807 ± 0.0104 N=28
Relative Pituitary Weight (% of brain weight) ^e	0.5045 ††† ± 0.0108 N=53 ^{l,j}	0.5067 ± 0.0129 N=24 ^l	0.4860 ± 0.0168 N=26 ^h	0.4850 ± 0.0120 N=28	0.5206 ± 0.0149 N=25 ^l	0.4706 ± 0.0133 N=28	0.5415 ± 0.0181 N=25 ^{h,j}	0.5511 ± 0.0143 N=27 ^h
Relative Thyroid Weight (% of brain weight) ^e	0.5005 ± 0.0136 N=54 ^l	0.5100 ± 0.0205 N=25 ^l	0.5064 ± 0.0212 N=24 ^{h,j}	0.5136 ± 0.0201 N=28	0.4761 ± 0.0235 N=27 ^l	0.4728 ± 0.0231 N=28	0.5258 ± 0.0224 N=25 ^{h,j}	0.5416 ± 0.0195 N=26 ^{h,j}
Relative Liver Weight (% of brain weight) ^e #	402.7943 † ± 7.1359 N=55	409.0285 ± 6.1242 N=28	408.6273 ± 8.7243 N=26 ^h	407.7808 ± 8.9500 N=28	408.9095 ± 10.1287 N=28	406.1776 ± 9.6890 N=28	474.4852 bbb ± 16.7024 N=26 ^h	398.5323 ± 9.6997 N=27 ^h
Relative Spleen Weight (% of brain weight) ^e	20.9792 ± 0.6396 N=55	21.3827 ± 0.6663 N=27 ^f	20.2941 ± 0.7746 N=26 ^h	19.9385 ± 0.9175 N=28	21.0789 ± 0.9004 N=28	20.9191 ± 1.2543 N=28	20.2891 ± 0.7982 N=26 ^h	20.3566 ± 0.6827 N=27 ^h
Relative Right Kidney Weight (% of brain weight) ^e #	72.5446 †† ± 1.2692 N=55	76.4391 ± 2.2309 N=28	75.3272 ± 2.0220 N=26 ^h	75.7404 ± 1.4715 N=28	80.0437 bb ± 2.4597 N=28	76.9866 ± 2.0238 N=28	85.2927 bbb ± 2.7458 N=26 ^h	77.5062 p ± 1.4968 N=27 ^h
Relative Left Kidney Weight (% of brain weight) ^e #	70.1410 ††† ± 1.3307 N=55	75.6764 p ± 2.1673 N=28	72.6529 ± 1.5892 N=26 ^h	72.8094 ± 1.2604 N=28	78.4640 bb ± 2.2781 N=28	74.5338 ± 2.0129 N=28	82.8048 bbb ± 2.2351 N=26 ^h	75.2641 bb ± 1.3586 N=27 ^h

Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 6 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Paired Adrenal Gland Weight (% of brain weight) ^e	1.3400 ± 0.0458 N=53 ^f	1.5279 ± 0.1013 N=28	1.2925 ± 0.0688 N=25 ^{f,h}	1.3262 ± 0.0788 N=25 ^{f,k}	1.3420 ± 0.0669 N=26 ^f	1.3302 ± 0.0777 N=27 ^f	1.3262 ± 0.0780 N=25 ^{f,h}	1.4600 ± 0.0910 N=26 ^{f,h}
Relative Paired Testis Weight (% of brain weight) ^e	51.0047 ± 0.8834 N=55	50.6343 ± 1.4152 N=28	51.1120 ± 1.1445 N=26 ^h	49.0587 ± 1.1412 N=28	51.8956 ± 1.2112 N=28	50.1612 ± 1.4951 N=28	48.0603 ± 1.1546 N=26 ^h	49.9409 ± 1.3197 N=26 ^{f,h}
Relative Paired Epididymis Weight (% of brain weight) ^e	21.5835 ‡ ± 0.3094 N=55	21.7692 ± 0.3896 N=28	21.0550 ± 0.4300 N=26 ^h	20.9199 ± 0.3535 N=28	21.7165 ± 0.3462 N=27 ^f	21.0171 ± 0.5122 N=28	20.0324 * ± 0.3813 N=26 ^h	20.6344 ± 0.4199 N=27 ^h
Relative Seminal Vesicles with Coagulating Gland Weight (% of brain weight) ^e #	68.4790 ± 1.5429 N=55	73.6834 ± 2.9385 N=28	72.8249 ± 4.2018 N=24 ^{h,l}	67.1878 ± 2.1133 N=28	69.6680 ± 3.1026 N=25 ^l	71.7202 ± 2.6432 N=28	63.5155 ± 2.0408 N=25 ^{h,l}	68.7545 ± 3.1977 N=27 ^h
Relative Ventral Prostate Weight (% of brain weight) ^e	5.1414 ± 0.2801 N=55	6.1572 ± 0.5415 N=28	5.8623 ± 0.5417 N=25 ^{f,h}	5.3840 ± 0.4167 N=28	5.9832 ± 0.4973 N=28	5.3599 ± 0.5360 N=28	4.7998 ± 0.4053 N=25 ^{f,h}	4.7245 ± 0.4183 N=27 ^h
Relative Dorsolateral Prostate Weight (% of brain weight) ^e	8.9207 ± 0.3466 N=54 ^f	9.1388 ± 0.4600 N=27 ^f	9.6494 ± 0.7262 N=26 ^h	9.5504 ± 0.6743 N=28	8.6793 ± 0.4965 N=28	8.3339 ± 0.5335 N=28	8.8294 ± 0.5262 N=25 ^{f,h}	8.0633 ± 0.5858 N=27 ^h
Relative Prostate Weight (% of brain weight) ^e	14.0042 ± 0.4365 N=54 ^m	15.3933 ± 0.7240 N=27 ^m	15.3837 ± 1.0367 N=25 ^{h,m}	14.9344 ± 0.8203 N=28	14.6624 ± 0.6878 N=28	13.6938 ± 0.7974 N=28	13.6292 ± 0.7921 N=25 ^{h,m}	12.7877 ± 0.7936 N=27 ^h

Table 31 Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 7 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Percent Motile Sperm ^e	45.0 ± 1.4 N=55	48.0 ± 2.0 N=28	45.0 ± 1.8 N=27	44.2 ± 2.1 N=28	45.9 ± 2.4 N=28	43.1 ± 1.9 N=28	49.6 ± 2.1 N=27	52.0 ± 1.5 N=28*
Percent Progressively Motile Sperm ^e	41.6 ± 1.3 N=55	43.6 ± 1.7 N=28	40.5 ± 1.8 N=27	40.9 ± 1.9 N=28	41.4 ± 2.2 N=28	38.4 ± 1.8 N=28	45.0 ± 2.1 N=27	46.6 ± 1.5 N=28
Epididymal Sperm Concentration (10 ⁶ /g) ^e	1806.03 ± 54.52 N=54 ^o	1820.57 ± 80.87 N=28	1866.21 ± 96.66 N=27	1795.04 ± 80.09 N=28	1757.56 ± 69.53 N=28	1812.84 ± 85.27 N=28	1701.81 ± 68.72 N=27	1596.23 ± 76.13 N=28
Spermatid Head Concentration (10 ⁶ /g) ^e	247.56 ± 11.84 N=55	230.99 ± 12.39 N=28	232.07 ± 12.98 N=27	228.23 ± 16.81 N=28	237.53 ± 14.37 N=28	250.96 ± 14.16 N=28	221.42 ± 12.67 N=27	233.40 ± 14.37 N=28
Daily Sperm Production per Testis (10 ⁶ /testis/day) ^e	7.00 ± 0.38 N=55	6.56 ± 0.45 N=28	6.59 ± 0.42 N=27	6.42 ± 0.53 N=28	6.77 ± 0.45 N=28	7.17 ± 0.52 N=28	5.96 ± 0.41 N=27	6.34 ± 0.40 N=28
Efficiency of Daily Sperm Production (10 ⁶ /g. testis/day) ^e	51.15 ± 2.45 N=55	47.73 ± 2.56 N=28	47.95 ± 2.68 N=27	47.16 ± 3.47 N=28	49.08 ± 2.97 N=28	51.85 ± 2.93 N=28	45.75 ± 2.62 N=27	48.22 ± 2.97 N=28
Percent Abnormal Sperm ^o	2.02 ± 0.08 N=55	2.13 ± 0.15 N=28	1.97 ± 0.14 N=27	2.26 ± 0.14 N=28	2.07 ± 0.15 N=28	2.25 ± 0.16 N=28	2.01 ± 0.12 N=27	2.16 ± 0.11 N=28

non statistically

Table 31. Summary and Statistical Analysis of the F₁ Parental Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 8 of 8)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups
- ^bMale 1353 was found dead on study day 35
- ^cMale 1275 was found dead on study day -13 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period)
- ^dMale 1201 was euthanized moribund on study day -10 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period).
- ^eReported as the mean \pm S E M
- ^fDecrease in N is due to one or more weights being statistical outliers and, therefore, they were excluded.
- ^gDecrease in N is due to one sacrifice weight inadvertently not being recorded.
- ^hDecrease in N is due to not all of the brain tissue being present at time of weighing.
- ⁱDecrease in N is due to one pituitary being lost at the time of necropsy.
- ^jDecrease in N is due to part or all of one or more organs not being present in the tissue cup at the time of weighing the fixed organ
- ^kDecrease in N is due to one of the adrenal glands being lost prior to weighing and, therefore the paired adrenal gland weight could not be obtained
- ^lDecrease in N is due to one or more pairs of seminal vesicles being nicked prior to weighing and, therefore, an accurate weight could not be obtained.
- ^mDecrease in N is due to either the ventral or dorsolateral prostate weight being missing and, therefore, the total prostate weight could not be calculated.
- ⁿDecrease in N is due to one sacrifice weight being a statistical outlier and, therefore, it was excluded
- ^oDecrease in N is due to the frozen cauda sample not being present at the time the epididymal sperm concentration measurements were done
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects
- [†] $p < 0.05$; ANOVA Test
- ^{††} $p < 0.01$; ANOVA Test.
- ^{†††} $p < 0.001$, ANOVA Test.
- ^{*} $p < 0.05$; Dunnett's Test.
- ^{**} $p < 0.01$; Dunnett's Test.
- ^{***} $p < 0.001$, Dunnett's Test.
- [†] $p < 0.05$; Wald Chi-square Test for overall treatment effect in robust regression model.
- ^{††} $p < 0.01$; Wald Chi-square Test for overall treatment effect in robust regression model.
- ^{†††} $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
- ^b $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model.
- ^{bb} $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model.
- ^{bbb} $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model

Table 32. Summary of the F₁ Parental Male Macroscopic and Microscopic Necropsy Findings (page 1 of 4)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Alopecia: around eye, right		1						
back above tail		1						
multiple areas	1					1		
nose	1	5	1	3	2	3	3	1
Kidney: hydronephrosis, bilateral		2	2		2	1	1	3
hydronephrosis, left	3		2			1		
hydronephrosis, right	4		3	1	3	1	1	2
Kidneys pale							1	
Liver pale							1	
Penis. 5 x 3 mm firm subcutaneous mass adjacent to							1	
Prostate, Dorsal reduced in size		1		1				1
Prostate: reduced in size					1			
Seminal Vesicle: atrophied, left	1							
reduced in size, left	1					1		
reduced in size, right								1
Seminal Vesicles reduced in size					1			
Sore(s): neck		1						
neck and ears						1		
Spleen: enlarged						1		
Tail: tip necrotic		1						
Thin fur. multiple areas							1	

UNSCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Liver: pale							1	
Testis: undescended, bilateral							1	

Table 32 Summary of the F₁ Parental Male Macroscopic and Microscopic Necropsy Findings (page 2 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>ADRENAL GLAND</u>								
Number Examined	55	10	10	10	10	10	10	10
Hyperplasia, Spindle Cell	7	1		2			2	4
Vacuolization, Cytoplasmic, Medulla	1							
<u>COAGULATING GLAND^b</u>								
Number Examined	55	12	12	10	10	12	13 ^c	15
No Findings								
<u>EPIDIDYMIS^b</u>								
Number Examined	55	12	12	10	10	12	14	15
Exfoliated Germ Cells	1				1	1		
Infiltrative Cell, Mononuclear Cell	3							
<u>KIDNEY</u>								
Number Examined	55	10	10	10	10	11	10	11
Cyst, Cortex	4	1	1	2	1	2		1
Cyst, Medulla	2	1						
Hydronephrosis, Bilateral			1		1		1	1
Hydronephrosis, Unilateral	5		2		1	3	1	2
Infiltrative Cell, Mononuclear Cell	5	1		1	2	1	1	
Inflammation, Chronic	1			1		1		
Inflammation, Pelvis, Chronic			1					
Inflammation, Tubulointerstitial, Medulla	4			1	1	1		1
Mineralization, Papillae	4				1		1	1
Nephropathy	6	2		1	2		4	1
Regeneration, Renal Tubule	1							

Table 32. Summary of the F₁ Parental Male Macroscopic and Microscopic Necropsy Findings (page 3 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
LIVER								
Number Examined	55	10	10	10	10	10	10	10
Hypertrophy, Hepatocyte, Centriobular	7			4	2	1	6	
Infiltrative Cell, Mononuclear Cell	3							
Necrosis, Hepatocyte, Focal	3						1	
PITUITARY								
Number Examined	54 ^c	8 ^c	10	10	10	9 ^c	10	10
Cyst, Pars Distalis			1					1
PROSTATE, DORSOLATERAL^b								
Number Examined	55	12	12	10	10	11 ^c	13 ^c	15
Infiltrative Cell, Mononuclear Cell	1		1					1
Inflammation, Chronic							1	
PROSTATE, VENTRAL^b								
Number Examined	55	11 ^c	12	10	10	12	13 ^c	15
Infiltrative Cell, Mononuclear Cell	1			2			1	
SEMINAL VESICLES^b								
Number Examined	55	12	12	10	10	12	12 ^c	15
Inflammation, Chronic			1					
SKIN^d								
Number Examined	1	1					1	
Necrosis		1						
SKIN, NOSE^d								
Number Examined		1		1			1	
No Findings								

Table 32 Summary of the F₁ Parental Male Macroscopic and Microscopic Necropsy Findings (page 4 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>SPLEEN</u>								
Number Examined	55	10	10	9 ^c	10	10	10	10
Hematopoietic Cell Proliferation	2					1	1	1
<u>TESTIS^b</u>								
Number Examined	55	12	12	10	10	12	12	14
Degeneration, Seminiferous Tubule	4	1	1	1		2		1
<u>THYROID</u>								
Number Examined	55	9 ^c	10	10	9 ^c	10	10	10
Cyst, Follicle		1			1		1	1
Ectopic Thymus	7	1	2				1	1

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^bIncludes males with suspected reduced fertility

^cThere was not a section of this tissue available for evaluation for one or more males.

^dIncludes only those males with a macroscopic necropsy finding for this tissue.

Table 44 Summary and Statistical Analysis of F₁ Reproductive and Lactational Indexes for the F₂ Litters (page 1 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. Animals on Study								
Males	56	28	28	28	28	28	28	28
Females	56	28	28	28	28	28	28	28
No. Females Paired	56	28	27 ^b	28	28	28	27 ^c	28
No. Females that Mated	55	27	25	28	28	28	25	25
Mating Index (no. females that mated/no. females paired)	98.2	96.4	92.6	100.0	100.0	100.0	92.6	89.3
No. of Pregnant Females	55	26	25	28	28	27	24	21
Fertility Index (no. pregnant females/no. females that mated)	100.0	96.3	100.0	100.0	100.0	96.4	96.0	84.0
No. of Females with Live Litters (pnd 0)	55	25 ^d	25	27 ^e	27 ^f	24 ^g	24	19 ^h
Gestational Index (no. females with live litters/no. females pregnant)	100.0	96.2	100.0	100.0 ^e	96.4	92.3 ^g	100.0	90.5
No. Males Paired	55	28	27	28	28	28	27	28
No. Males that Mated	54	27	25	28	28	28	25	25
Mating Index (no. males that mated/no. males paired)	98.2	96.4	92.6	100.0	100.0	100.0	92.6	89.3

Table 44. Summary and Statistical Analysis of F₁ Reproductive and Lactational Indexes for the F₂ Litters (page 2 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. Males Siring Litters	54	26	25	28	28	27	24	21
Fertility Index (no. males siring litters/no. males that mated)	100.0 ££	96.3	100.0	100.0	100.0	96.4	96.0	84.0 ☐☐
Pregnancy Index (no. pregnant females/no. males that mated)	101.9 ^l	96.3	100.0	100.0	100.0	96.4	96.0	84.0
<hr/>								
Precoital Interval (days) ^{j,k}								
#	2.4	3.8	2.3	2.7	2.8	2.6	2.6	2.7
	± 0.2	± 0.6	± 0.2	± 0.2	± 0.3	± 0.3	± 0.4	± 0.4
	N=53	N=25	N=25	N=25	N=26	N=25	N=25	N=25
Gestational Length (days) ^{j,l}								
	19.0 †††	18.9	18.9	19.1	19.0	19.0	19.3*	19.4**
	± 0.0	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1
	N=53	N=24	N=25	N=24	N=26	N=23	N=24	N=20
No. Live Litters								
Postnatal Day 0	55	25	25	27	27	24	24	19
Postnatal Day 4	55	25	25	27	26 ^m	24	23 ⁿ	19
Postnatal Day 7	55	25	25	27	25 ^o	24	23	19
Postnatal Day 14	54 ^p	25	25	27	24 ^q	24	23	19
Postnatal Day 21	54	25	25	27	24	21 ^r	23	19
No. Implantation Sites per Litter ^l								
	12.5	12.3	12.8	13.4	12.6	12.6	12.1	10.8
	± 0.4	± 0.5	± 0.2	± 0.6	± 0.6	± 0.6	± 0.6	± 0.5
	N=55	N=26	N=25	N=28	N=28	N=26 ^s	N=24	N=21
Percent Postimplantation Loss per Litter ^l								
	6.0	6.2	4.2	5.3	9.7	15.3	9.4	14.4
	± 1.5	± 3.8	± 1.2	± 1.6	± 3.8	± 5.5	± 3.3	± 5.1
	N=55	N=26	N=25	N=27	N=28	N=26 ^s	N=24	N=21

Table 44 Summary and Statistical Analysis of F₁ Reproductive and Lactational Indexes for the F₂ Litters (page 3 of 5)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Number of Live Pups on Postnatal Day 0 ⁱ	12.4 ± 0.4 N=55	12.8 ± 0.3 N=25	12.6 ± 0.3 N=25	12.4 ± 0.5 N=27	12.4 ± 0.5 N=27	12.8 ± 0.6 N=24	11.5 ± 0.6 N=24	10.1 ± 0.7** N=20
Number of Dead Pups on Postnatal Day 0 ⁱ	0.2 ± 0.1 N=55	0.1 ± 0.1 N=25	0.2 ± 0.1 N=25	0.2 ± 0.1 N=27	0.1 ± 0.1 N=27	0.2 ± 0.1 N=24	0.0 ± 0.0 N=24	0.2 ± 0.1 N=20
Total Number of Pups on Postnatal Day 0 ^j	12.6 ± 0.4 N=55	13.0 ± 0.3 N=25	12.8 ± 0.3 N=25	12.6 ± 0.5 N=27	12.6 ± 0.5 N=27	12.9 ± 0.6 N=24	11.5 ± 0.6 N=24	10.3 ± 0.7** N=20
Stillbirth Index (no. dead on pnd 0/total no. on pnd 0) ^j	1.6 ± 0.7 N=55	0.9 ± 0.7 N=25	1.6 ± 0.8 N=25	1.4 ± 0.8 N=27	0.9 ± 0.6 N=27	2.2 ± 1.4 N=24	0.0 ± 0.0 N=24	5.8 ± 5.0 N=20
Live Birth Index (no. live on pnd 0/total no. on pnd 0) ^j	98.4 ± 0.7 N=55	99.1 ± 0.7 N=25	98.4 ± 0.8 N=25	98.6 ± 0.8 N=27	99.1 ± 0.6 N=27	97.8 ± 1.4 N=24	100.0 ± 0.0 N=24	94.2 ± 5.0 N=20
4 Day Survival Index (no. surviving 4 days/no. live on pnd 0) ^j	98.5 ± 0.8 N=55	98.2 ± 0.6 N=25	98.5 ± 1.5 N=25	98.6 ± 0.6 N=27	95.0 ± 3.7 N=27	99.1 ± 0.5 N=24	93.4 ± 4.2 N=24	98.2 ± 1.0 N=19
7 Day Survival Index (no. surviving 7 days/no. live on pnd 4) ^j	99.2 ± 0.6 N=55	100.0 ± 0.0 N=25	100.0 ± 0.0 N=25	99.3 ± 0.7 N=27	100.0 ± 0.0 N=25	100.0 ± 0.0 N=24	98.6 ± 1.4 N=23	95.3 ± 4.7 N=19

Table 44. Summary and Statistical Analysis of F₁ Reproductive and Lactational Indexes for the F₂ Litters (page 4 of 5)

	Bisphenol A (ppm in the feed)						17β-Estradiol (ppm in the feed)	
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
14 Day Survival Index (no. surviving 14 days/no. live on pnd 7) ^j	98.3	100.0	100.0	99.5	100.0	100.0	99.6	100.0
	± 1.5	± 0.0	± 0.0	± 0.5	± 0.0	± 0.0	± 0.4	± 0.0
	N=54	N=25	N=25	N=27	N=24	N=24	N=23	N=19
21 Day Survival Index (no. surviving 21 days/no. live on pnd 14) ^j	99.6 †††	100.0	100.0	100.0	100.0	86.6 ***	100.0	100.0
	± 0.3	± 0.0	± 0.0	± 0.0	± 0.0	± 6.9	± 0.0	± 0.0
	N=54	N=25	N=25	N=27	N=24	N=24	N=23	N=19
Lactational Index (no. surviving 21 days/no. live on pnd 4) ^j	97.2 ‡	100.0	100.0	98.9	100.0	86.6 *	98.1	95.3
	± 1.6	± 0.0	± 0.0	± 1.1	± 0.0	± 6.9	± 1.5	± 4.7
	N=54	N=25	N=25	N=27	N=24	N=24	N=23	N=19

Table 44. Summary and Statistical Analysis of F₁ Reproductive and Lactational Indexes for the F₂ Litters (page 5 of 5)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups
- ^bFemale 1270 was found dead on study day -12 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period)
- ^cFemale 1212 was euthanized moribund on study day -11 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period).
- ^dFemale 1016 was pregnant but had implantation sites only.
- ^eFemale 1068 was found dead on gestational day 20 (study day 77). She had 22 retained fetuses and one resorption in utero. She was not included in the calculation of the gestational index since she died prior to delivery.
- ^fFemale 1090 was pregnant but had implantation sites only.
- ^gFemales 1040 and 1148 were pregnant but had implantation sites only. Female 1218 was euthanized moribund on study day 69 and had retained fetuses in utero. She was not included in the calculation of the gestational index since she died prior to delivery.
- ^hFemale 1166 was pregnant but had implantation sites only. Female 1350 was pregnant but had litters of all dead pups
- ⁱDue to the death of male 1353, male 1403 was paired with two different females, both of which were pregnant
- ^jReported as the mean \pm S.E. M.; pnd=postnatal day. All indexes are the average percent per litter
- ^kPrecoital interval could only be calculated for those females for which a plug was detected.
- ^lGestational length could not be calculated for females that were pregnant, but for which a plug was never detected.
- ^mThe entire litter for female 1206 was found dead or missing and presumed dead on the afternoon of postnatal day 0.
- ⁿThe entire litter for female 1116 was found dead or missing and presumed dead on the afternoon of postnatal day 0.
- ^oFemale 1444 was euthanized moribund on postnatal day 6 and, therefore, her litter was euthanized on postnatal day 6.
- ^pFemale 1082 was found dead on postnatal day 8 and, therefore, her litter was euthanized on postnatal day 8
- ^qFemale 1220 was found dead on postnatal day 12 and, therefore, her litter was euthanized on postnatal day 12.
- ^rThe entire litter for females 1030 and 1088 was found dead or missing and presumed dead on or before postnatal day 19. The entire litter for female 1178 was found dead or missing and presumed dead on or before postnatal day 18.
- ^sThe exact number of implantation sites could not be determined for female 1218 due to the condition of the uterus with retained fetuses present.
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.
- ^{££} $p < 0.05$; Chi-Square Test
- ^{ΦΦ} $p < 0.01$; Fishers' Exact Test.
- [‡] $p < 0.05$, ANOVA Test.
- ^{‡‡‡} $p < 0.001$; ANOVA Test.
- ^{*} $p < 0.05$; Dunnett's Test.
- ^{**} $p < 0.01$; Dunnett's Test.
- ^{***} $p < 0.001$; Dunnett's Test.

Table 45. Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 1 of 6)

	Bisphenol A (ppm in the feed)							17 β -Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
No. Live Litters								
Postnatal Day 0	55	25	25	27	27	24	24	19
Postnatal Day 4	55	25	25	27	26 ^b	24	23 ^c	19
Postnatal Day 7	55	25	25	27	25 ^d	24	23	19
Postnatal Day 14	54 ^e	25	25	27	24 ^f	24	23	19
Postnatal Day 21	54	25	25	27	24	21 ^g	23	19
Average Number of Live Pups per Litter (pnd 0) ^h	12.4	12.8	12.6	12.4	12.4	12.8	11.5	10.6
	\pm 0.4	\pm 0.3	\pm 0.3	\pm 0.5	\pm 0.5	\pm 0.6	\pm 0.6	\pm 0.5
	N=55	N=25	N=25	N=27	N=27	N=24	N=24	N=19
Average Number of Live Pups per Litter (pnd 4) ^h	12.2	12.6	12.4	12.2	12.2	12.6	11.2	10.4
	\pm 0.4	\pm 0.3	\pm 0.4	\pm 0.5	\pm 0.5	\pm 0.6	\pm 0.6	\pm 0.5
	N=55	N=25	N=25	N=27	N=26	N=24	N=23	N=19
Average Number of Live Pups per Litter (pnd 7) ^h	9.4	10.0	9.9	9.6	9.7	9.5	9.2	8.8
	\pm 0.2	\pm 0.0	\pm 0.1	\pm 0.3	\pm 0.3	\pm 0.3	\pm 0.3	\pm 0.5
	N=55	N=25	N=25	N=27	N=25	N=24	N=23	N=19
Average Number of Live Pups per Litter (pnd 14) ^h	9.3	10.0	9.9	9.5	9.7	9.5	9.1	8.8
	\pm 0.3	\pm 0.0	\pm 0.1	\pm 0.3	\pm 0.3	\pm 0.3	\pm 0.3	\pm 0.5
	N=54	N=25	N=25	N=27	N=24	N=24	N=23	N=19
Average Number of Live Pups per Litter (pnd 21) ^h	9.2	10.0	9.9	9.5	9.7	9.4	9.1	8.8
	\pm 0.3	\pm 0.0	\pm 0.1	\pm 0.3	\pm 0.3	\pm 0.4	\pm 0.3	\pm 0.5
	N=54	N=25	N=25	N=27	N=24	N=21	N=23	N=19

Table 45. Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 2 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Average Male Pup Anogenital Distance (mm) per Litter (pnd 0) ^h	1.36 ± 0.02 N=55	1.39 ± 0.03 N=25	1.34 ± 0.03 N=25	1.27 ± 0.03 N=27	1.34 ± 0.03 N=27	1.32 ± 0.04 N=24	1.33 ± 0.03 N=24	1.29 ± 0.04 N=19
Average Adjusted Male Pup Anogenital Distance (mm) per Litter (pnd 0) ⁱ	1.36 ± 0.02 N=55	1.40 ± 0.03 N=25	1.35 ± 0.03 N=25	1.27 ± 0.03 N=27	1.33 ± 0.03 N=27	1.32 ± 0.03 N=24	1.32 ± 0.03 N=24	1.28 ± 0.04 N=19
Average Female Pup Anogenital Distance (mm) per Litter (pnd 0) ^h	# 0.67 † ± 0.01 N=55	0.70 ‡ ± 0.01 N=25	0.66 ± 0.01 N=25	0.66 ± 0.01 N=27	0.66 ± 0.01 N=27	0.71 ± 0.02 N=24	0.66 ± 0.02 N=24	0.68 ± 0.01 N=19
Average Adjusted Female Pup Anogenital Distance (mm) per Litter (pnd 0) ^j	0.68 Σ ± 0.01 N=55	0.71 σ ± 0.01 N=25	0.66 ± 0.01 N=25	0.66 ± 0.01 N=27	0.66 ± 0.01 N=27	0.71 ± 0.02 N=24	0.66 ± 0.02 N=24	0.67 ± 0.01 N=19
Average Pup Body Weight (g) per Litter (pnd 0) ^h	1.63 ± 0.02 N=55	1.61 ± 0.02 N=25	1.62 ± 0.02 N=25	1.64 ± 0.04 N=27	1.65 ± 0.02 N=27	1.65 ± 0.03 N=24	1.68 ± 0.04 N=24	1.72 ± 0.04 N=19
Average Male Body Weight (g) per Litter (pnd 0) ^h	1.67 ± 0.02 N=55	1.64 ± 0.02 N=25	1.65 ± 0.02 N=25	1.69 ± 0.03 N=27	1.69 ± 0.02 N=27	1.68 ± 0.03 N=24	1.71 ± 0.04 N=24	1.74 ± 0.05 N=19
Average Female Body Weight (g) per Litter (pnd 0) ^h	1.60 ± 0.02 N=55	1.57 ± 0.02 N=25	1.59 ± 0.02 N=25	1.61 ± 0.04 N=27	1.62 ± 0.02 N=27	1.63 ± 0.03 N=24	1.65 ± 0.04 N=24	1.69 ± 0.05 N=19

Table 45. Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 3 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Average Pup Body Weight (g) per Litter (pnd 4) ^h								
#	2.95	2.95	2.94	3.00	3.01	2.92	3.03	3.19
	± 0.05	± 0.05	± 0.05	± 0.11	± 0.06	± 0.08	± 0.13	± 0.12
	N=55	N=25	N=25	N=27	N=26	N=24	N=23	N=19
Average Male Body Weight (g) per Litter (pnd 4) ^h								
#	3.02	3.03	3.00	3.07	3.09	2.94	3.09	3.23
	± 0.05	± 0.05	± 0.05	± 0.10	± 0.06	± 0.08	± 0.12	± 0.12
	N=55	N=25	N=25	N=27	N=26	N=24	N=23	N=19
Average Female Body Weight (g) per Litter (pnd 4) ^h								
#	2.89	2.89	2.86	2.93	2.95	2.88	2.95	3.15
	± 0.05	± 0.05	± 0.05	± 0.11	± 0.06	± 0.08	± 0.14	± 0.13
	N=55	N=25	N=25	N=27	N=26	N=24	N=23	N=19
Average Pup Body Weight (g) per Litter (pnd 7) ^h								
#	4.75	4.83	4.79	4.79	4.95	4.78	4.61	4.68
	± 0.08	± 0.09	± 0.07	± 0.17	± 0.07	± 0.11	± 0.18	± 0.17
	N=55	N=25	N=25	N=27	N=25	N=24	N=23	N=19
Average Male Body Weight (g) per Litter (pnd 7) ^h								
#	4.84	4.93	4.86	4.88	5.02	4.81	4.71	4.72
	± 0.08	± 0.09	± 0.08	± 0.17	± 0.07	± 0.11	± 0.17	± 0.16
	N=55	N=25	N=25	N=27	N=25	N=24	N=23	N=19
Average Female Body Weight (g) per Litter (pnd 7) ^h								
#	4.64	4.73	4.71	4.70	4.88	4.75	4.49	4.70
	± 0.09	± 0.09	± 0.06	± 0.17	± 0.07	± 0.12	± 0.19	± 0.17
	N=55	N=25	N=25	N=27	N=25	N=24	N=23	N=18 ^j

Table 45 Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 4 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Average Pup Body Weight (g) per Litter (pnd 14) ^h	7.55 ± 0.13 N=54	7.41 ± 0.16 N=25	7.56 ± 0.10 N=25	7.64 ± 0.31 N=27	7.67 ± 0.21 N=24	7.68 ± 0.22 N=24	7.20 ± 0.29 N=23	7.27 ± 0.26 N=19
Average Male Body Weight (g) per Litter (pnd 14) ^h	7.66 ± 0.13 N=53 ^k	7.49 ± 0.16 N=25	7.64 ± 0.11 N=25	7.63 ± 0.33 N=27	7.66 ± 0.21 N=24	7.72 ± 0.24 N=24	7.29 ± 0.28 N=23	7.23 ± 0.26 N=19
Average Female Body Weight (g) per Litter (pnd 14) ^h	7.45 ± 0.13 N=54	7.34 ± 0.16 N=25	7.49 ± 0.10 N=25	7.59 ± 0.31 N=27	7.66 ± 0.21 N=24	7.63 ± 0.21 N=24	7.09 ± 0.30 N=23	7.32 ± 0.28 N=18 ^l
Average Pup Body Weight (g) per Litter (pnd 21) ^h	11.02 ± 0.27 N=54	10.47 ± 0.25 N=25	10.75 ± 0.17 N=25	10.90 ± 0.48 N=27	11.00 ± 0.36 N=24	11.03 ± 0.37 N=21	10.03 ± 0.49 N=23	10.80 ± 0.54 N=19
Average Male Body Weight (g) per Litter (pnd 21) ^h	11.30 ± 0.28 N=53 ^k	10.69 ± 0.26 N=25	10.98 ± 0.19 N=25	10.99 ± 0.56 N=27	11.09 ± 0.37 N=24	11.20 ± 0.42 N=21	10.22 ± 0.48 N=23	10.84 ± 0.56 N=19
Average Female Body Weight (g) per Litter (pnd 21) ^h	10.73 ± 0.27 N=54	10.24 ± 0.25 N=25	10.50 ± 0.18 N=25	10.73 ± 0.46 N=27	10.86 ± 0.35 N=24	10.83 ± 0.34 N=21	9.79 ± 0.50 N=23	10.82 ± 0.57 N=18 ^l

Table 45 Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 5 of 6)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Percent Male Pups per Litter (pnd 0) ^h	49.5	48.2	47.7	44.9	50.8	51.2	49.0	45.0
	± 2.1	± 3.1	± 2.8	± 2.1	± 2.6	± 2.9	± 3.3	± 3.8
	N=55	N=25	N=25	N=27	N=27	N=24	N=24	N=19
Percent Male Pups per Litter (pnd 4) ^h	50.0	46.6	48.8	46.0	51.0	52.1	47.0	44.9
	± 2.0	± 2.9	± 2.5	± 2.2	± 2.7	± 3.0	± 3.3	± 3.9
	N=55	N=25	N=25	N=27	N=26	N=24	N=23	N=19
Percent Male Pups per Litter (pnd 7) ^h	50.7	48.0	48.3	47.5	50.8	51.2	45.1	47.6
#	± 1.7	± 2.3	± 1.3	± 1.9	± 2.1	± 1.7	± 2.5	± 4.4
	N=55	N=25	N=25	N=27	N=25	N=24	N=23	N=19
Percent Male Pups per Litter (pnd 14) ^h	50.1	48.0	48.3	47.6	51.2	51.2	45.3	47.6
	± 1.9	± 2.3	± 1.3	± 1.8	± 2.1	± 1.7	± 2.5	± 4.4
	N=54	N=25	N=25	N=27	N=24	N=24	N=23	N=19
Percent Male Pups per Litter (pnd 21) ^h	50.3	48.0	48.3	47.6	51.2	50.9	45.3	47.6
	± 1.9	± 2.3	± 1.3	± 1.8	± 2.1	± 2.0	± 2.5	± 4.4
	N=54	N=25	N=25	N=27	N=24	N=21	N=23	N=19

Table 45. Summary and Statistical Analysis of the F₂ Litter Size, Pup Anogenital Distance, Pup Body Weights and Percent Male Pups During Lactation
(page 6 of 6)

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups.

^bThe entire litter for female 1206 was found dead or missing and presumed dead on the afternoon of postnatal day 0

^cThe entire litter for female 1116 was found dead or missing and presumed dead on the afternoon of postnatal day 0.

^dFemale 1444 was euthanized moribund on postnatal day 6 and, therefore, her litter was euthanized on postnatal day 6.

^eFemale 1082 was found dead on postnatal day 8 and, therefore, her litter was euthanized on postnatal day 8

^fFemale 1220 was found dead on postnatal day 12 and, therefore, her litter was euthanized on postnatal day 12.

^gThe entire litter for females 1030 and 1088 was found dead or missing and presumed dead on or before postnatal day 19 The entire litter for female 1178 was found dead or missing and presumed dead on or before postnatal day 18.

^hReported as the mean \pm S.E.M , pnd=postnatal day

ⁱReported as the adjusted mean \pm S.E.M (body weight as covariate).

^jDecrease in N is due to one litter having only male pups.

^kDecrease in N is due to one litter having only female pups.

[#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.

[†] $p < 0.05$; Wald Chi-square Test for overall treatment effect in robust regression model.

^P $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model

^Σ $p < 0.05$; Wald Chi-square Test for overall treatment effect in robust regression model with body weight as a covariate.

^σ $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model with body weight as a covariate.

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 1 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. F₂ Male Pups Necropsied with Organ Weights^b	106	50	50	52	48	41	46	37
Total No. F₂ Male Pups Necropsied^b	249	120	120	124	118	100	96	76
Sacrifice Body Weight (g)^c	11.18 ± 0.26 N=249	10.88 ± 0.30 N=120	10.97 ± 0.21 N=120	10.84 ± 0.26 N=124	11.06 ± 0.25 N=118	11.00 ± 0.40 N=100	10.07 ± 0.42 N=96	10.33 ± 0.57 N=76
Anogenital Distance (mm)^c	7.5 ± 0.2 N=249	7.3 ± 0.2 N=120	7.4 ± 0.2 N=120	7.3 ± 0.2 N=124	7.8 ± 0.2 N=118	7.5 ± 0.4 N=100	7.2 ± 0.2 N=96	6.5 ± 0.5 N=76
Adjusted Anogenital Distance (mm)^d	7.4 ± 0.1 N=249	7.3 ± 0.2 N=120	7.3 ± 0.2 N=120	7.2 ± 0.2 N=124	7.7 ± 0.2 N=118	7.4 ± 0.2 N=100	7.6 ± 0.2 N=96	6.8 ± 0.2 N=76
Brain Weight (g)^c	0.4507 ± 0.0039 N=105 ^e	0.4377 ± 0.0055 N=50	0.4533 ± 0.0044 N=50	0.4456 ± 0.0054 N=52	0.4465 ± 0.0056 N=48	0.4555 ± 0.0060 N=41	0.4453 ± 0.0046 N=46	0.4367 ± 0.0056 N=37
Thymus Weight (g)^c	0.0772 ± 0.0026 N=106	0.0736 ± 0.0033 N=50	0.0790 ± 0.0028 N=50	0.0725 ± 0.0033 N=52	0.0726 ± 0.0030 N=48	0.0769 ± 0.0035 N=41	0.0692 ± 0.0038 N=46	0.0639 ± 0.0041 N=37
Liver Weight (g)^c	0.6416 ± 0.0200 N=106	0.6254 ± 0.0243 N=50	0.5959 ± 0.0170 N=50	0.6116 ± 0.0237 N=52	0.6164 ± 0.0259 N=48	0.6245 ± 0.0259 N=41	0.5995 ± 0.0365 N=46	0.6062 ± 0.0378 N=37

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 2 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Spleen Weight (g) ^c	0.0883 Γ + 0.0039 N=106	0.0784 + 0.0044 N=50	0.0778 ± 0.0039 N=50	0.0824 ± 0.0058 N=51 ^e	0.0791 ± 0.0050 N=48	0.0802 ± 0.0060 N=41	0.0638 δδδ + 0.0051 N=46	0.0711 δδ + 0.0055 N=37
Right Kidney Weight (g) ^c	0.1028 ± 0.0025 N=106	0.0992 ± 0.0034 N=50	0.1000 ± 0.0026 N=50	0.0983 ± 0.0042 N=52	0.1032 ± 0.0035 N=48	0.1034 ± 0.0031 N=41	0.0963 ± 0.0049 N=46	0.0928 ± 0.0051 N=37
Left Kidney Weight (g) ^c	0.0976 ± 0.0024 N=106	0.0948 ± 0.0032 N=50	0.0953 ± 0.0027 N=50	0.0918 ± 0.0035 N=52	0.0997 ± 0.0032 N=47 ^e	0.0977 ± 0.0028 N=41	0.0923 ± 0.0046 N=46	0.0885 ± 0.0046 N=37
Paired Testis Weight (g) ^c	0.0594 ΓΓΓ + 0.0015 N=106	0.0573 ± 0.0022 N=50	0.0591 ± 0.0021 N=50	0.0571 ± 0.0026 N=52	0.0612 ± 0.0022 N=48	0.0598 ± 0.0020 N=41	0.0525 δ + 0.0031 N=46	0.0427 δδδ ± 0.0024 N=37
Paired Epididymis Weight (g) ^c	0.0215 ΓΓΓ ± 0.0006 N=106	0.0206 ± 0.0011 N=50	0.0223 ± 0.0015 N=50	0.0199 ± 0.0013 N=52	0.0224 ± 0.0012 N=48	0.0208 ± 0.0010 N=41	0.0200 ± 0.0009 N=46	0.0134 δδδ ± 0.0007 N=37
Seminal Vesicles with Coagulating Gland Weight (g) ^c	0.0124 ΓΓ ± 0.0006 N=105 ^e	0.0126 ± 0.0009 N=50	0.0119 ± 0.0010 N=50	0.0121 ± 0.0010 N=52	0.0121 ± 0.0007 N=48	0.0107 ± 0.0007 N=41	0.0103 δ ± 0.0007 N=46	0.0093 δδδ ± 0.0006 N=37
Relative Brain Weight (% of sacrifice weight) ^c	4.0092 ± 0.0793 N=105 ^e	4.0165 ± 0.0961 N=50	4.1073 ± 0.0660 N=50	4.1867 ± 0.1144 N=52	4.0481 ± 0.1092 N=48	4.1092 ± 0.0942 N=41	4.5468 ± 0.2021 N=46	4.1509 ± 0.2295 N=37

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 3 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% of sacrifice weight) ^C	0.6691 IT ± 0.0162 N=106	0.6654 ± 0.0268 N=50	0.7102 ± 0.0207 N=50	0.6481 ± 0.0178 N=52	0.6417 ± 0.0217 N=48	0.6789 ± 0.0259 N=41	0.6724 ± 0.0236 N=46	0.5712 δδ ± 0.0227 N=37
Relative Liver Weight (% of sacrifice weight) ^C	5.5306 ± 0.0713 N=106	5.6073 ± 0.1287 N=50	5.3440 ± 0.0979 N=50	5.5169 ± 0.0782 N=52	5.4082 ± 0.1098 N=48	5.5217 ± 0.1347 N=41	5.7417 ± 0.1027 N=46	5.4281 ± 0.1301 N=37
Relative Spleen Weight (% of sacrifice weight) ^C	0.7541 IT ± 0.0228 N=106	0.6982 ± 0.0327 N=50	0.6901 ± 0.0259 N=50	0.7252 ± 0.0400 N=51 ^e	0.6836 ± 0.0290 N=48	0.6989 ± 0.0392 N=41	0.6017 δδδ ± 0.0362 N=46	0.6272 δδ ± 0.0318 N=37
Relative Right Kidney Weight (% of sacrifice weight) ^C	0.8937 IT ± 0.0118 N=106	0.8907 ± 0.0172 N=50	0.8981 ± 0.0168 N=50	0.8853 ± 0.0142 N=52	0.9147 ± 0.0186 N=48	0.9205 ± 0.0162 N=41	0.9355 ± 0.0196 N=46	0.8396 δ ± 0.0195 N=37
Relative Left Kidney Weight (% of sacrifice weight) ^C	0.8495 ITT ± 0.0116 N=106	0.8548 ± 0.0196 N=50	0.8560 ± 0.0163 N=50	0.8294 ± 0.0088 N=52	0.8852 ± 0.0146 N=47 ^e	0.8683 ± 0.0118 N=41	0.8985 δ ± 0.0169 N=46	0.8029 δ ± 0.0181 N=37
Relative Paired Testis Weight (% of sacrifice weight) ^C	0.5185 ITT ± 0.0082 N=106	0.5156 ± 0.0155 N=50	0.5285 ± 0.0129 N=50	0.5153 ± 0.0148 N=52	0.5431 ± 0.0106 N=48	0.5333 ± 0.0136 N=41	0.5032 ± 0.0144 N=46	0.3880 δδδ ± 0.0123 N=37
Relative Paired Epididymis Weight (% of sacrifice weight) ^C	0.1895 ITT ± 0.0050 N=106	0.1839 ± 0.0071 N=50	0.1978 ± 0.0108 N=50	0.1783 ± 0.0101 N=52	0.1979 ± 0.0072 N=48	0.1872 ± 0.0098 N=41	0.1987 ± 0.0077 N=46	0.1238 δδδ ± 0.0058 N=37
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight) ^C	0.1067 IT ± 0.0039 N=105 ^e	0.1129 ± 0.0077 N=50	0.1057 ± 0.0086 N=50	0.1073 ± 0.0063 N=52	0.1070 ± 0.0052 N=48	0.0948 ± 0.0054 N=41	0.1033 ± 0.0064 N=46	0.0857 δδ ± 0.0053 N=37

Table 48. Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 4 of 9)

	Bisphenol A (ppm in the feed)							17 β -Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Relative Thymus Weight (% of brain weight) ^c	17.0861 \pm 0.5370 N=105 ^f	16.8183 \pm 0.7671 N=50	17.3927 \pm 0.5751 N=50	16.1581 \pm 0.6723 N=52	16.1809 \pm 0.5866 N=48	16.8056 \pm 0.7188 N=41	15.4330 \pm 0.7654 N=46	14.5220 \pm 0.8397 N=37
Relative Liver Weight (% of brain weight) ^c	142.0414 \pm 4.0598 N=105 ^f	143.2193 \pm 5.5961 N=50	131.2123 \pm 3.0794 N=50	136.7656 \pm 4.5933 N=52	137.7344 \pm 4.9415 N=48	137.1780 \pm 5.4997 N=41	133.5738 \pm 7.3390 N=46	137.8986 \pm 7.6715 N=37
Relative Spleen Weight (% of brain weight) ^c	19.5029 Γ \pm 0.8192 N=105 ^f	17.9640 \pm 1.0396 N=50	17.0838 δ \pm 0.7609 N=50	18.3607 \pm 1.2709 N=51 ^e	17.7160 \pm 1.0761 N=48	17.5293 \pm 1.2578 N=41	14.1742 $\delta\delta\delta$ \pm 1.0933 N=46	16.0880 δ \pm 1.1344 N=37
Relative Right Kidney Weight (% of brain weight) ^c	22.7365 \pm 0.4970 N=105 ^f	22.6952 \pm 0.7752 N=50	22.0402 \pm 0.5232 N=50	21.9307 \pm 0.8118 N=52	23.0956 \pm 0.6658 N=48	22.7144 \pm 0.6062 N=41	21.4768 \pm 0.9540 N=46	21.0853 \pm 0.9759 N=37
Relative Left Kidney Weight (% of brain weight) ^c	21.5891 \pm 0.4691 N=105 ^f	21.7456 \pm 0.7536 N=50	21.0220 \pm 0.5397 N=50	20.4919 \pm 0.6509 N=52	22.3459 \pm 0.5925 N=47 ^e	21.4653 \pm 0.5566 N=41	20.5933 \pm 0.8787 N=46	20.1329 \pm 0.8913 N=37
Relative Paired Testis Weight (% of brain weight) ^c	13.1936 $\Gamma\Gamma\Gamma$ \pm 0.2918 N=105 ^f	13.1058 \pm 0.4916 N=50	13.0286 \pm 0.4351 N=50	12.7494 \pm 0.5378 N=52	13.7199 \pm 0.4626 N=48	13.1309 \pm 0.3912 N=41	11.6957 δ \pm 0.6370 N=46	9.7194 $\delta\delta\delta$ \pm 0.4819 N=37
Relative Paired Epididymis Weight (% of brain weight) ^c	4.7799 $\Gamma\Gamma\Gamma$ \pm 0.1272 N=105 ^f	4.7028 \pm 0.2327 N=50	4.8727 \pm 0.2990 N=50	4.4192 \pm 0.2875 N=52	5.0068 \pm 0.2257 N=48	4.5570 \pm 0.1995 N=41	4.4744 \pm 0.1872 N=46	3.0503 $\delta\delta\delta$ \pm 0.1423 N=37

Table 48. Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 5 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Relative Seminal Vesicles with Coagulating Gland Weight (% of brain weight) ^c	2.7393 Γ ± 0.1272 N=104 ^{e,f}	2.8654 ± 0.1954 N=50	2.5988 ± 0.2193 N=50	2.6886 ± 0.2085 N=52	2.6944 ± 0.1398 N=48	2.3325 δ ± 0.1421 N=41	2.3137 δ ± 0.1479 N=46	2.1197 $\delta\delta$ ± 0.1313 N=37
No. F ₂ Female Pups Necropsied with Organ Weights ^b	104	50	50	54	47	41	46	36
Total No. F ₂ Female Pups Necropsied ^b	249	130	127	133	114	97	114	91
Sacrifice Body Weight (g) ^c	10.62 ± 0.20 N=247 ^g	10.38 ± 0.29 N=130	10.47 ± 0.20 N=127	10.47 ± 0.27 N=133	10.72 ± 0.25 N=114	10.84 ± 0.29 N=97	9.71 ± 0.42 N=114	10.75 ± 0.39 N=91
Anogenital Distance (mm) ^c	4.6 ± 0.1 N=249	4.4 ± 0.1 N=130	4.6 ± 0.1 N=127	4.5 ± 0.1 N=133	4.8 ± 0.1 N=114	4.7 ± 0.2 N=97	4.6 ± 0.1 N=114	4.6 ± 0.2 N=91
Adjusted Anogenital Distance (mm) ^d	4.5 ± 0.1 N=247 ^g	4.5 ± 0.1 N=130	4.6 ± 0.1 N=127	4.5 ± 0.1 N=133	4.7 ± 0.1 N=114	4.6 ± 0.1 N=97	4.8 ± 0.1 N=114	4.5 ± 0.1 N=91
Brain Weight (g) ^c	0.4448 Γ ± 0.0037 N=103 ^e	0.4378 ± 0.0045 N=50	0.4476 ± 0.0032 N=49 ^e	0.4488 ± 0.0036 N=54	0.4495 ± 0.0051 N=47	0.4468 ± 0.0071 N=41	0.4246 $\delta\delta$ ± 0.0056 N=46	0.4408 ± 0.0053 N=36
Thymus Weight (g) ^c	0.0764 Γ ± 0.0027 N=104	0.0727 ± 0.0031 N=50	0.0781 ± 0.0031 N=50	0.0736 ± 0.0036 N=54	0.0750 ± 0.0027 N=47	0.0804 ± 0.0034 N=41	0.0702 ± 0.0042 N=46	0.0616 $\delta\delta$ ± 0.0037 N=36

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 6 of 9)

	Bisphenol A (ppm in the feed)							17 β -Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed) 0.5
Liver Weight (g) ^c	0.5990 ± 0.0168 N=104	0.5933 ± 0.0212 N=50	0.5716 ± 0.0153 N=50	0.6085 ± 0.0250 N=54	0.6043 ± 0.0203 N=47	0.5973 ± 0.0237 N=41	0.5694 ± 0.0366 N=46	0.5607 ± 0.0342 N=36
Spleen Weight (g) ^c	0.0831 F ± 0.0034 N=104	0.0790 ± 0.0042 N=50	0.0781 ± 0.0037 N=50	0.0825 ± 0.0050 N=53 ^e	0.0802 ± 0.0042 N=47	0.0793 ± 0.0044 N=41	0.0605 555 ± 0.0049 N=46	0.0714 ± 0.0066 N=36
Right Kidney Weight (g) ^c	0.0988 ± 0.0025 N=104	0.0986 ± 0.0032 N=49 ^e	0.0998 ± 0.0024 N=50	0.1017 ± 0.0041 N=54	0.1018 ± 0.0026 N=47	0.1034 ± 0.0035 N=41	0.0933 ± 0.0050 N=46	0.0918 ± 0.0047 N=36
Left Kidney Weight (g) ^c	0.0961 ± 0.0024 N=104	0.0937 ± 0.0032 N=50	0.0956 ± 0.0024 N=50	0.0958 ± 0.0038 N=54	0.1015 ± 0.0023 N=47	0.0999 ± 0.0037 N=41	0.0893 ± 0.0047 N=46	0.0893 ± 0.0042 N=36
Paired Ovary Weight (g) ^c	0.0117 ± 0.0004 N=104	0.0106 ± 0.0006 N=50	0.0113 ± 0.0006 N=50	0.0120 ± 0.0009 N=54	0.0116 ± 0.0006 N=47	0.0107 ± 0.0005 N=41	0.0097 ± 0.0007 N=46	0.0109 ± 0.0006 N=36
Uterus with Cervix and Vagina Weight (g) ^c	0.0481 ITT ± 0.0027 N=104	0.0453 ± 0.0023 N=50	0.0486 ± 0.0027 N=50	0.0570 ± 0.0086 N=54	0.0520 ± 0.0040 N=46 ^h	0.0408 ± 0.0025 N=41	0.0463 ± 0.0049 N=46	0.1736 555 ± 0.0124 N=36
Relative Brain Weight (% sacrifice weight) ^c	4.1712 ± 0.0728 N=102 ^{e,l}	4.1621 ± 0.0979 N=50	4.2602 ± 0.0777 N=49 ^e	4.2116 ± 0.1146 N=54	4.1106 ± 0.0762 N=47	4.1154 ± 0.0886 N=41	4.5021 ± 0.1913 N=46	4.2513 ± 0.2153 N=36

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 7 of 9)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% sacrifice weight) ^C	0.6970 ITT ± 0.0173 N=103 ⁱ	0.6754 ± 0.0214 N=50	0.7372 ± 0.0271 N=50	0.6670 ± 0.0182 N=54	0.6800 ± 0.0221 N=47	0.7284 ± 0.0209 N=41	0.7056 ± 0.0302 N=46	0.5666 δδδ ± 0.0267 N=36
Relative Liver Weight (% sacrifice weight) ^C	5.4859 ITT ± 0.0628 N=103 ⁱ	5.5162 ± 0.0925 N=50	5.3856 ± 0.0798 N=50	5.5321 ± 0.797 N=54	5.4433 ± 0.0946 N=47	5.3961 ± 0.1052 N=41	5.6602 ± 0.1083 N=46	5.1273 δδ ± 0.0940 N=36
Relative Spleen Weight (% sacrifice weight) ^C	0.7558 ITT ± 0.0209 N=103 ⁱ	0.7302 ± 0.0311 N=50	0.7309 ± 0.0260 N=50	0.7409 ± 0.0301 N=53 ^e	0.7176 ± 0.0300 N=47	0.7112 ± 0.0281 N=41	0.5942 δδδ ± 0.0329 N=46	0.6385 δ ± 0.0436 N=36
Relative Right Kidney Weight (% sacrifice weight) ^C	0.9094 ITT ± 0.0125 N=103 ⁱ	0.9229 ± 0.0167 N=49 ^e	0.9426 ± 0.0162 N=50	0.9282 ± 0.0170 N=54	0.9242 ± 0.0180 N=47	0.9397 ± 0.0198 N=41	0.9401 ± 0.0153 N=46	0.8490 δδ ± 0.0153 N=36
Relative Left Kidney Weight (% sacrifice weight) ^C	0.8853 ITT ± 0.0131 N=103 ⁱ	0.8723 ± 0.0171 N=50	0.9023 ± 0.0145 N=50	0.8721 ± 0.0118 N=54	0.9228 ± 0.0177 N=47	0.9068 ± 0.0195 N=41	0.9004 ± 0.0196 N=46	0.8288 δδ ± 0.0157 N=36
Relative Paired Ovary Weight (% sacrifice weight) ^C	0.1071 ± 0.0031 N=103 ⁱ	0.0982 ± 0.0042 N=50	0.1071 ± 0.0062 N=50	0.1077 ± 0.0055 N=54	0.1057 ± 0.0057 N=47	0.0983 ± 0.0050 N=41	0.0979 ± 0.0052 N=46	0.1021 ± 0.0042 N=36
Relative Uterus with Cervix and Vagina Weight (% sacrifice weight) ^C	0.4374 ITT ± 0.0190 N=103 ⁱ	0.4231 ± 0.0183 N=50	0.4543 ± 0.0221 N=50	0.4859 ± 0.0374 N=54	0.4579 ± 0.0281 N=46 ^h	0.3668 δ ± 0.0188 N=41	0.4504 ± 0.0291 N=46	1.5846 δδδ ± 0.1014 N=36

Table 48 Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 8 of 9)

	Bisphenol A (ppm in the feed)						17β-Estradiol (ppm in the feed)	
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Thymus Weight (% brain weight) ^C	16.9963 Γ ± 0.5264 N=103 ^f	16.5426 ± 0.6280 N=50	17.3572 ± 0.6491 N=49 ^f	16.3484 ± 0.7204 N=54	16.6665 ± 0.5695 N=47	18.0413 ± 0.7174 N=41	16.3955 ± 0.9060 N=46	13.9720 δδ ± 0.8258 N=36
Relative Liver Weight (% brain weight) ^C	134.0571 ± 3.2615 N=103 ^f	135.0152 ± 4.0576 N=50	128.1619 ± 3.4627 N=49 ^f	135.3156 ± 4.9705 N=54	134.2745 ± 4.0382 N=47	133.4179 ± 4.2809 N=41	132.9571 ± 7.3214 N=46	126.7012 ± 7.0147 N=36
Relative Spleen Weight (% brain weight) ^C	18.5672 Γ ± 0.6651 N=103 ^f	17.9821 ± 0.8994 N=50	17.3488 ± 0.7777 N=49 ^f	18.3074 ± 1.0216 N=53 ^e	17.8298 ± 0.9137 N=47	17.6886 ± 0.8646 N=41	14.0993 δδδ ± 1.0731 N=46	16.1033 ± 1.4317 N=36
Relative Right Kidney Weight (% brain weight) ^C	22.1593 ± 0.4661 N=103 ^f	22.5054 ± 0.6386 N=49 ^e	22.3294 ± 0.5083 N=49 ^f	22.6236 ± 0.8056 N=54	22.6724 ± 0.5032 N=47	23.1056 ± 0.5795 N=41	21.8409 ± 0.9771 N=46	20.7436 ± 0.9239 N=36
Relative Left Kidney Weight (% brain weight) ^C	21.5594 ± 0.4579 N=103 ^f	21.3409 ± 0.6369 N=50	21.4132 ± 0.5179 N=49 ^f	21.3160 ± 0.7511 N=54	22.5965 ± 0.4456 N=47	22.3223 ± 0.6457 N=41	20.9098 ± 0.9269 N=46	20.1901 ± 0.8194 N=36
Relative Paired Ovary Weight (% brain weight) ^C	2.6201 ± 0.0923 N=103 ^f	2.4045 ± 0.1177 N=50	2.5017 ± 0.1408 N=49 ^f	2.6645 ± 0.1921 N=54	2.5854 ± 0.1375 N=47	2.3971 ± 0.1121 N=41	2.2831 ± 0.1468 N=46	2.4748 ± 0.1085 N=36
Relative Uterus with Cervix and Vagina Weight (% brain weight) ^C	10.7112 ΓΓ ± 0.5534 N=103 ^f	10.3029 ± 0.5025 N=50	10.8651 ± 0.5929 N=49 ^f	12.4797 ± 1.7122 N=54	11.4486 ± 0.8343 N=46 ^h	9.0618 ± 0.5095 N=41	10.7501 ± 1.0533 N=46	39.1009 δδδ ± 2.7502 N=36

Table 48. Summary and Statistical Analysis of the F₂ Male and Female Pup Anogenital Distance and Organ Weights on Postnatal Day 21 (page 9 of 9)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2) See Appendix III for the comparison of the two control groups.
- ^bAll pups had a macroscopic necropsy examination with sacrifice weight recorded and anogenital distance measured. A maximum of two pups per sex per litter also had specified organ weights recorded.
- ^cReported as the mean \pm S.E.M. (adjusted for intralitter correlation)
- ^dReported as the mean \pm S.E.M. (adjusted for intralitter correlation and sacrifice weight as covariate)
- ^eDecrease in N is due to one weight being a statistical outlier and, therefore, it was excluded.
- ^fDecrease in N is due to one brain weight being excluded because it was a statistical outlier.
- ^gDecrease in N is due to two sacrifice weights inadvertently not being recorded.
- ^hDecrease in N is due to all or part of the organ/tissue from one animal being lost at necropsy prior to weighing.
- ⁱDecrease in N is due to one sacrifice weight inadvertently not being recorded
- ^I_p<0.05, Wald Chi-square Test for overall treatment effect for correlated data.
- ^{II}_p<0.01; Wald Chi-square Test for overall treatment effect for correlated data.
- ^{III}_p<0.001; Wald Chi-square Test for overall treatment effect for correlated data
- ^δ_p<0.05; Individual t-test for pairwise comparison to control for correlated data
- ^{δδ}_p<0.01; Individual t-test for pairwise comparison to control for correlated data.
- ^{δδδ}_p<0.001, Individual t-test for pairwise comparison to control for correlated data.
- ^ƒ_p<0.05, Wald Chi-square Test for overall treatment effect in robust regression model with correlated data and sacrifice weight as a covariate
- ^{ff}_p<0.01; Individual t-test for pairwise comparisons to control in robust regression model with correlated data and sacrifice weight as a covariate

Table 49 Summary of the F₂ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 1 of 5)

MACROSCOPIC FINDINGS

Sex ^a	Finding	Bisphenol A (ppm in the feed)						17 β -Estradiol (ppm in the feed)	
		0 ^b	0.018	0.18	1.8	30	300	3500	0.5
F	Cervix: hard and thickened								1
	thickened	1							
	Ovary: cyst, left	1					1	1	
	fluid filled cyst, left					2			
	fluid filled cyst, right	1							
	Stomach: misshaped and small								1
	Tail: black and constricted		1						
	black, tip							1	
	constricted	1							
	injured	1							
	missing, tip, cage accident	1							
	necrotic		1						
	necrotic, tip		1					1	
	short		1						
	Thymus: reduced in size	1							
	Uterus: enlarged								1
	enlarged and fluid filled, bilateral								3
	enlarged and walls thickened								1
	enlarged, bilateral							1	
	fluid filled								18
fluid filled, bilateral	1			2			1	55	
walls thickened								2	
Vagina: enlarged							1		
enlarged, open and thickened								3	
open	1			1			1	28	
open and thickened							1	41	
thickened					1	1	1		
M	Kidney: hydronephrosis, right				1		1	1	
	Liver: pale	2							

Table 49 Summary of the F₂ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 2 of 5)

MACROSCOPIC FINDINGS

Sex ^a	Finding	Bisphenol A (ppm in the feed)						17β-Estradiol (ppm in the feed)	
		0 ^b	0.018	0.18	1.8	30	300	3500	0.5
M	Tail: distal 1/3 flat, cage accident						1		
	necrotic, tip		1			1		1	
	necrotic, tip and dark red 2 cm anterior to tip		1						
	pinched, cage accident	1							
	Testis: undescended							1	
	undescended, bilateral	8	1	7	6	1	10	14	36
	undescended, left	3	1	4	7	2	3	1	7
	undescended, right	3	2	5	2	3	2	3	1
Thymus reduced in size	1								

240 100 100 124 118 100 118 76
 16% 50%

MICROSCOPIC FINDINGS FOR THE FEMALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
BRAIN								
Number Examined	50	25	25	27	23	20	23	18
No Findings								
CERVIX								
Number Examined	88 ^c	46 ^c	48 ^c	48 ^c	36 ^c	38 ^c	36 ^c	23 ^c
Epithelium, Keratinized								1
KIDNEY								
Number Examined	50	25	25	27	23	20	23	18
Regeneration, Renal Tubule	8	1	1	3	4	4	2	1
LIVER								
Number Examined	50	25	25	27	23	20	23	18
Cytoplasmic Alteration, Hepatocyte, Centriobular	4		1	2	1	3	3	1
Infiltrative Cell, Mononuclear Cell	2							

Table 49. Summary of the F₂ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 3 of 5)

MICROSCOPIC FINDINGS FOR THE FEMALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>OVARY</u>								
Number Examined	104	48 ^c	49 ^c	54	47	41	46	36
Cyst, Paraovarian			1	1	1			
<u>SPLEEN</u>								
Number Examined	50	25	25	27	22 ^c	20	23	18
No Findings								
<u>STOMACH</u>								
Number Examined								1
No Findings								
<u>TAIL^d</u>								
Number Examined	2	3				1	1	
Deformity		1						
Necrosis		2				1	1	
<u>THYMUS</u>								
Number Examined	49 ^c	25	25	26 ^c	22 ^c	20	22 ^c	18
Atrophy	1							
Cyst			1					
<u>UTERINE HORN</u>								
Number Examined	104	50	50	54	46 ^c	41	48	84
Dilatation, Lumen, Bilateral	3			2				82
<u>VAGINA</u>								
Number Examined	101 ^c	48 ^c	50	54	44 ^c	41	47 ^c	76 ^c
Epithelium, Keratinized	10	1	1	4	4	5	13	74

Table 49. Summary of the F₂ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 4 of 5)

MICROSCOPIC FINDINGS FOR THE MALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>BRAIN</u>								
Number Examined	53	25	25	25	24	20	23	18
No Findings								
<u>COAGULATING GLAND</u>								
Number Examined	100 ^c	46 ^c	43 ^c	50 ^c	43 ^c	40 ^c	41 ^c	31 ^c
No Findings								
<u>EPIDIDYMIS</u>								
Number Examined	106	50	50	52	48	41	46	35 ^c
No Findings								
<u>KIDNEY</u>								
Number Examined	53	25	25	26	24	21	23	18
Cyst, Cortex	1							
Cyst, Medulla								1
Dilatation, Renal Tubule	1							
Hydronephrosis, Unilateral				2		1	1	
Regeneration, Renal Tubule	8	3	3	3	3	3	3	4
<u>LIVER</u>								
Number Examined	54	25	25	25	24	20	23	18
Cytoplasmic Alteration, Hepatocyte, Centriobular Infiltrative Cell, Mononuclear Cell	6	1	1	1	1	2	9	1
	2							1
<u>SEMINAL VESICLE</u>								
Number Examined	104 ^c	45 ^c	46 ^c	50 ^c	44 ^c	40 ^c	45 ^c	32 ^c
No Findings								
<u>SPLEEN</u>								
Number Examined	53	25	25	25	24	20	23	18
No Findings								

Table 49. Summary of the F₂ Pup Macroscopic and Microscopic Necropsy Findings on Postnatal Day 21 (page 5 of 5)

MICROSCOPIC FINDINGS FOR THE MALE PUPS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^b	0.018	0.18	1.8	30	300	3500	0.5
<u>TAIL</u> ^d								
Number Examined		2			1			1
Necrosis		2			1			1
<u>TESTIS</u>								
Number Examined	114	53	61	55	51	49	57	66
Atrophy, Seminiferous Tubule, Unilateral	1					1	1	
Dilatation, Rete Testis	3				1	1		
Dilatation, Seminiferous Tubule, Unilateral	1				2	1		
Hypoplasia, Seminiferous Tubule	5	1	2	2		5	20	17
<u>THYMUS</u>								
Number Examined	53	24	25	25	23 ^c	20	23	17 ^c
Atrophy	1							

^aF is female and M is male.

^bCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^cThere was not a section of this tissue available for evaluation for one or more pups

^dIncludes only those pups with a macroscopic necropsy finding for this tissue.

Table 50 Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 1 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No of F ₁ Females at Scheduled Sacrifice	55 ^b	28	27 ^c	27 ^d	26 ^e	27 ^f	27 ^g	28
Sacrifice Body Weight (g) ^h	36.79 ††† ± 0.53 N=55	37.42 ± 0.80 N=28	36.21 ± 0.58 N=27	38.14 ± 0.56 N=27	36.29 ± 0.67 N=26	36.47 ± 0.74 N=27	35.24 ± 0.66 N=27	33.22 *** ± 0.81 N=28
Brain Weight (g) ^h	0.5355 ± 0.0050 N=54 ⁱ	0.5256 ± 0.0074 N=28	0.5372 ± 0.0081 N=26 ^j	0.5441 ± 0.0068 N=27	0.5300 ± 0.0073 N=24 ^l	0.5264 ± 0.0058 N=27	0.5153 ± 0.0079 N=27	0.5269 ± 0.0065 N=28
Pituitary Weight (g) ^h	0.0038 ††† ± 0.0001 N=54 ^k	0.0041 ± 0.0001 N=28	0.0039 ± 0.0001 N=27	0.0040 ± 0.0001 N=27	0.0038 ± 0.0001 N=23 ^{k,l}	0.0039 ± 0.0001 N=27	0.0034 ± 0.0001 N=26 ^k	0.0035 ± 0.0001 N=27 ^k
Thyroid Weight (g) ^h	0.0031 ± 0.0001 N=52 ^k	0.0032 ± 0.0001 N=27 ^k	0.0029 ± 0.0001 N=25 ^k	0.0032 ± 0.0001 N=25 ^k	0.0030 ± 0.0001 N=26	0.0032 ± 0.0001 N=25 ^k	0.0029 ± 0.0001 N=22 ^{k,l}	0.0030 ± 0.0001 N=25 ^{k,l}
Liver Weight (g) ^h	2.9392 ††† ± 0.0683 N=55	2.8893 ± 0.0967 N=28	2.8447 ± 0.0946 N=27	3.0892 ± 0.0917 N=27	2.8253 ± 0.0922 N=26	2.7762 ± 0.1125 N=27	3.1065 ± 0.1368 N=27	2.4147 *** ± 0.1239 N=28
Spleen Weight (g) ^h	0.1385 ± 0.0040 N=55	0.1377 ± 0.0084 N=28	0.1344 ± 0.0050 N=27	0.1491 ± 0.0070 N=27	0.1395 ± 0.0061 N=26	0.1359 ± 0.0079 N=27	0.1300 ± 0.0071 N=27	0.1433 ± 0.0075 N=28
Right Kidney Weight (g) ^h	0.3256 ††† ± 0.0059 N=55	0.3171 ± 0.0056 N=28	0.3244 ± 0.0073 N=27	0.3543 * ± 0.0068 N=27	0.3271 ± 0.0094 N=26	0.3240 ± 0.0088 N=27	0.3395 ± 0.0099 N=27	0.2989 * ± 0.0086 N=28

Table 50. Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 2 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Left Kidney Weight (g) ^h	0.3217 ††† ± 0.0052 N=55	0.3039 ± 0.0064 N=28	0.3119 ± 0.0077 N=27	0.3426 ± 0.0075 N=27	0.3143 ± 0.0083 N=26	0.3215 ± 0.0078 N=27	0.3255 ± 0.0096 N=26 ^m	0.2920 * ± 0.0076 N=28
Paired Adrenal Gland Weight (g) ^h	0.0142 ± 0.0006 N=55	0.0142 ± 0.0007 N=28	0.0131 ± 0.0006 N=27	0.0149 ± 0.0008 N=26 ⁿ	0.0134 ± 0.0008 N=26	0.0133 ± 0.0007 N=27	0.0134 ± 0.0007 N=26 ⁱ	0.0128 ± 0.0008 N=28
Paired Ovary Weight (g) ^h	0.0438 ± 0.0015 N=55	0.0469 ± 0.0037 N=28	0.0430 ± 0.0022 N=27	0.0462 ± 0.0025 N=27	0.0458 ± 0.0030 N=26	0.0425 ± 0.0020 N=27	0.0458 ± 0.0026 N=27	0.0431 ± 0.0032 N=28
Uterus with Cervix and Vagina Weight (g) ^h	0.3374 †† ± 0.0136 N=55	0.3667 ± 0.0253 N=28	0.3261 ± 0.0171 N=27	0.3553 ± 0.0225 N=27	0.2788 ± 0.0164 N=25 ^l	0.2979 ± 0.0202 N=27	0.3207 ± 0.0202 N=27	0.3916 ± 0.0165 N=28
Relative Brain Weight (% sacrifice weight) ^h	1.4697 †† ± 0.0233 N=54 ^l	1.4191 ± 0.0321 N=28	1.4976 ± 0.0298 N=26 ^j	1.4321 ± 0.0221 N=27	1.4547 ± 0.0280 N=24 ⁱ	1.4540 ± 0.0245 N=27	1.4753 ± 0.0351 N=27	1.6078 ** ± 0.0390 N=28
Relative Pituitary Weight (% sacrifice weight) ^h #	0.0103 ± 0.0002 N=54 ^k	0.0110 ± 0.0004 N=28	0.0107 ± 0.0004 N=27	0.0106 ± 0.0003 N=27	0.0105 ± 0.0002 N=23 ^{k,l}	0.0106 ± 0.0003 N=27	0.0098 ± 0.0003 N=26 ^k	0.0107 ± 0.0003 N=27 ^k
Relative Thyroid Weight (% sacrifice weight) ^h	0.0084 ± 0.0002 N=52 ^k	0.0085 ± 0.0004 N=27 ^k	0.0080 ± 0.0003 N=25 ^k	0.0083 ± 0.0003 N=25 ^k	0.0082 ± 0.0003 N=26	0.0089 ± 0.0004 N=25 ^k	0.0082 ± 0.0004 N=22 ^{k,l}	0.0092 ± 0.0004 N=25 ^{k,l}

Table 50. Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Liver Weight (% sacrifice weight) ^h								
#	7.9508 ††	7.6899	7.8153	8.0776	7.7559	7.5492	8.7272 b	7.1704 bb
	± 0.1110	± 0.1743	± 0.1765	± 0.1677	± 0.1632	± 0.1895	± 0.2969	± 0.2444
	N=55	N=28	N=27	N=27	N=26	N=27	N=27	N=28
Relative Spleen Weight (% sacrifice weight) ^h								
	0.3785	0.3701	0.3745	0.3910	0.3848	0.3729	0.3692	0.4327
	± 0.0108	± 0.0232	± 0.0160	± 0.0173	± 0.0155	± 0.0225	± 0.0182	± 0.0212
	N=55	N=28	N=27	N=27	N=26	N=27	N=27	N=28
Relative Right Kidney Weight (% sacrifice weight) ^h								
	0.8886 ††	0.8519	0.9000	0.9301	0.9027	0.8883	0.9632 *	0.9028
	± 0.0148	± 0.0137	± 0.0233	± 0.0145	± 0.0212	± 0.0164	± 0.0220	± 0.0217
	N=55	N=28	N=27	N=27	N=26	N=27	N=27	N=28
Relative Left Kidney Weight (% sacrifice weight) ^h								
	0.8778 ††	0.8167 *	0.8642	0.8994	0.8683	0.8830	0.9238	0.8820
	± 0.0125	± 0.0167	± 0.0219	± 0.0168	± 0.0193	± 0.0166	± 0.0199	± 0.0172
	N=55	N=28	N=27	N=27	N=26	N=27	N=26 ^m	N=28
Relative Paired Adrenal Gland Weight (% sacrifice weight) ^h								
	0.0392	0.0387	0.0366	0.0392	0.0375	0.0363	0.0380	0.0391
	± 0.0017	± 0.0023	± 0.0019	± 0.0021	± 0.0022	± 0.0019	± 0.0019	± 0.0024
	N=55	N=28	N=27	N=26 ⁿ	N=26	N=27	N=26 ^l	N=28
Relative Paired Ovary Weight (% sacrifice weight) ^h								
	0.1204	0.1262	0.1200	0.1215	0.1266	0.1172	0.1319	0.1313
	± 0.0047	± 0.0098	± 0.0070	± 0.0067	± 0.0082	± 0.0052	± 0.0089	± 0.0102
	N=55	N=28	N=27	N=27	N=26	N=27	N=27	N=28
Relative Uterus with Cervix and Vagina Weight (% sacrifice weight) ^h								
	0.9332 †††	1.0017	0.9094	0.9339	0.7818	0.8185	0.9262	1.2021 **
	± 0.0429	± 0.0791	± 0.0521	± 0.0588	± 0.0499	± 0.0551	± 0.0637	± 0.0606
	N=55	N=28	N=27	N=27	N=25 ⁱ	N=27	N=27	N=28

Table 50 Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 7)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Pituitary Weight (% brain weight) ^h	0.7101 †† ± 0.0148 N=53 ^{k,o}	0.7730 ± 0.0249 N=28	0.7129 ± 0.0202 N=26 ^l	0.7413 ± 0.0202 N=27	0.7304 ± 0.0214 N=22 ^{k,l,o}	0.7327 ± 0.0223 N=27	0.6699 ± 0.0228 N=26 ^k	0.6691 ± 0.0179 N=27 ^k
Relative Thyroid Weight (% brain weight) ^h	0.5754 ± 0.0132 N=51 ^{k,o}	0.6059 ± 0.0295 N=27 ^k	0.5405 ± 0.0206 N=24 ^{l,k}	0.5855 ± 0.0263 N=25 ^k	0.5718 ± 0.0229 N=24 ^o	0.6126 ± 0.0236 N=25 ^k	0.5587 ± 0.0241 N=22 ^{k,l}	0.5686 ± 0.0220 N=25 ^{k,l}
Relative Liver Weight (% brain weight) ^h #	550.6673 †† ± 13.4170 N=54 ^o	552.1234 ± 19.3247 N=28	528.3002 ± 19.5576 N=26 ^l	568.7770 ± 16.4011 N=27	543.6387 ± 17.1748 N=24 ^o	526.0807 ± 18.8332 N=27	606.2095 ± 28.1839 N=27	458.0715 ††† ± 22.8795 N=28
Relative Spleen Weight (% brain weight) ^h	25.9235 ± 0.7690 N=54 ^o	26.2557 ± 1.5956 N=28	25.0789 ± 1.0586 N=26 ^l	27.2799 ± 1.0860 N=27	26.8449 ± 1.2645 N=24 ^o	25.7612 ± 1.5100 N=27	25.3658 ± 1.4635 N=27	27.2683 ± 1.4540 N=28
Relative Right Kidney Weight (% brain weight) ^h	60.9225 †† ± 1.1639 N=54 ^o	60.6087 ± 1.2841 N=28	60.6874 ± 1.7299 N=26 ^l	65.1879 ± 1.1536 N=27	61.8369 ± 1.6642 N=24 ^o	61.4950 ± 1.4213 N=27	66.1765 * ± 2.0796 N=27	56.6570 ± 1.4560 N=28
Relative Left Kidney Weight (% brain weight) ^h #	60.2605 ††† ± 0.9837 N=54 ^o	58.0665 ± 1.3684 N=28	58.3449 ± 1.8512 N=26 ^l	62.9534 ± 1.1147 N=27	59.5841 ± 1.5074 N=24 ^o	61.0749 ± 1.3253 N=27	63.1294 ± 1.8871 N=26 ^m	55.3995 †† ± 1.2450 N=28
Relative Paired Adrenal Gland Weight (% brain weight) ^h	2.6748 ± 0.0968 N=54 ^o	2.7095 ± 0.1403 N=28	2.4346 ± 0.1123 N=26 ^l	2.7512 ± 0.1434 N=26 ⁿ	2.5077 ± 0.1200 N=24 ^o	2.5096 ± 0.1274 N=27	2.5935 ± 0.1114 N=26 ^l	2.4267 ± 0.1361 N=28

Table 50. Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 7)

	Bisphenol A (ppm in the feed)							17 β -Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Relative Paired Ovary Weight (% brain weight) ^h								
	8.1773	8.9132	8.0824	8.4943	8.7858	8.0628	8.8691	8.1243
	\pm 0.2494	\pm 0.7066	\pm 0.4713	\pm 0.4641	\pm 0.6839	\pm 0.3477	\pm 0.4701	\pm 0.5389
	N=54 ^o	N=28	N=26 ^l	N=27	N=24 ^o	N=27	N=27	N=28
Relative Uterus with Cervix and Vagina Weight (% brain weight) ^h								
	63.7169 $\ddagger\ddagger$	70.5348	60.5257	65.6227	51.8909	56.5189	62.8471	74.6404
	\pm 2.6827	\pm 5.2351	\pm 3.5263	\pm 4.3062	\pm 3.1752	\pm 3.7777	\pm 4.3188	\pm 3.2855
	N=54 ^o	N=28	N=26 ^l	N=27	N=23 ^{l, o}	N=27	N=27	N=28
Paired Ovarian Follicle Counts ^{h, p}								
	95.4						91.0	102.2
	\pm 5.1						\pm 6.8	\pm 7.6
	N=55						N=27	N=28

Table 50 Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 6 of 7)

	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>VAGINAL CYTOLOGY EVALUATION AT NECROPSY:^a</u>								
No. of F ₁ Females Evaluated	55 ^b	28	27 ^c	27 ^d	26 ^e	27 ^f	27 ^g	28
No. in Proestrus	0	0	0	2	0	0	0	0
Percent in Proestrus	0.00	0.00	0.00	7.41	0.00	0.00	0.00	0.00
No. in Estrus	15	11	6	7	5	5	10	8
Percent in Estrus	27.27	39.29	22.22	25.93	19.23	18.52	37.04	28.57
No. in Metestrus	0	0	1	1	2	1	0	3
Percent in Metestrus	0.00	0.00	3.70	3.70	7.69	3.70	0.00	10.71
No. in Diestrus	40	17	20	17	19	21	17	17
Percent in Diestrus	72.73	60.71	74.07	62.96	73.08	77.78	62.96	60.71
No. Stage Not Determined	0	0	0	0	0	0	0	0
No. No Cells Present ^f	0	0	0	0	0	0	0	0

Table 50 Summary and Statistical Analysis of the F₁ Female Organ Weights, Relative Organ Weights, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 7 of 7)

- ^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups.
- ^bFemale 1082 was found dead on postnatal day 8 (study day 87).
- ^cFemale 1270 was found dead on study day -12 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period).
- ^dFemale 1068 was found dead on gestational day 20 (study day 77).
- ^eFemale 1220 was found dead on postnatal day 12 (study day 89) and female 1444 was euthanized moribund on postnatal day 6 (study day 81).
- ^fFemale 1218 was euthanized moribund on study day 69.
- ^gFemale 1212 was euthanized moribund on study day -11 (study day 0 was first day of the prebreed period and negative study days were during the postwean holding period prior to the start of the prebreed period)
- ^hReported as the mean \pm S E M.
- ⁱDecrease in N is due to one or more weights being statistical outliers and, therefore, they were excluded
- ^jDecrease in N is due to not all of the brain tissue being present at time of weighing for one or more animals
- ^kDecrease in N is due to part or all of one or more organs not being present in the tissue cup at the time of weighing the fixed organ.
- ^lDecrease in N is due to all or part of one pituitary or one thyroid being lost at the time of weighing the fixed organ, therefore the fixed weight could not be obtained
- ^mDecrease in N is due to female 1404 not having a left kidney.
- ⁿDecrease in N is due to one of the adrenal glands being lost prior to weighing for one animal and, therefore the paired adrenal gland weight could not be obtained.
- ^oDecrease in N is due to one or more brain weights being statistical outliers and, therefore, they were excluded
- ^pOvarian follicle counts were done for all control females, all females in the 3500 ppm dose group and all females in the 0.5 ppm 17 β -Estradiol dose group.
- ^qFor presentation and statistical analysis purposes those females in two stages were pooled in the following manner: proestrus/estrus and estrus/proestrus were considered proestrus, estrus/metestrus and metestrus/estrus were considered estrus; metestrus/diestrus and diestrus/metestrus were considered metestrus; and diestrus/proestrus and proestrus/diestrus were considered diestrus. The females for which the stage could not be determined or no cells were present were not included in the statistical analysis.
- ^rThese smears did not contain sloughed cells or the cells washed off during processing and, therefore, they could not be evaluated.
- [#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects.
- ^{††} $p < 0.01$; ANOVA Test.
- ^{†††} $p < 0.001$, ANOVA Test.
- ^{*} $p < 0.05$; Dunnett's Test
- ^{**} $p < 0.01$; Dunnett's Test.
- ^{***} $p < 0.001$, Dunnett's Test.
- ^{††††} $p < 0.01$; Wald Chi-square Test for overall treatment effect in robust regression model
- ^{†††††} $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
- ^p $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model
- ^{pp} $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model.
- ^{ppp} $p < 0.001$, Individual t-test for pairwise comparisons to control in robust regression model
- [£] $p < 0.05$; Chi-Square Test.

Table 51. Summary of the F₁ Female Macroscopic and Microscopic Necropsy Findings (page 1 of 5)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Alopecia: above tail	1							
head				1				
head and nose								1
hip, right							1	
multiple areas				1				
multiple areas on back and sides				1				
neck				1				
nose					1		1	1
Cervix: enlarged and firm							1	
firm and thickened						1	2	
hard and thickened						2		3
Colon: impacted with feces						1		
Firm beige material under first two nipples, under arms and into neck bilateral						1		
Gall Bladder: enlarged						1		
Kidney: fluid filled cyst present where left kidney should have been							1	
Mass: 0.5 x 0.5 cm firm, subcutaneous, white pus filled above vaginal opening							1	
Ovary: cyst(s), bilateral		1	1				1	
cyst(s), blood filled, bilateral			1					
cyst(s), clear, bilateral				1	1		2	
cyst(s), clear, left		3		1	2		1	2
cyst(s), clear, right						2		1
cyst(s), fluid filled			1					
cyst(s), fluid filled, bilateral	3	1						1
cyst(s), fluid filled, left	3	2		1			2	2
cyst(s), fluid filled, right	1				1			
cyst(s), left	1			1			1	2
cyst(s), red fluid filled, left	1			1		3		
cyst(s), red fluid filled, right					1			
cyst(s), right	1							1

Table 51 Summary of the F₁ Female Macroscopic and Microscopic Necropsy Findings (page 2 of 5)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Small Intestine and Stomach. abnormally distended with food/ingesta						1		
Spleen enlarged						1		
Thin fur: right side		1						
Uterus: clear fluid filled, right horn					1			
cyst(s), clear, below ovary on left horn								1
enlarged and thickened, bilateral		1					1	
enlarged, bilateral								1
implantation sites extremely light		1					1	
implantation sites very light	1					1		2
resorption(s), free floating in right horn					1			
resorption(s), left and right horns						1		
resorption(s), left horn at ovarian end					1			
resorptions(s), left horn near cervix						1		
resorptions(s), near cervix		1						
resorption(s), right horn	1			1	1			
thickened, bilateral		1						
walls enlarged and thickened								1
Vagina: cyst(s)	1							
enlarged and thickened								1
thickened							1	2

UNSCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17 β -Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Stomach and Intestines: not otherwise specified					1			

Table 51 Summary of the F₁ Female Macroscopic and Microscopic Necropsy Findings (page 3 of 5)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>ADRENAL GLAND</u>								
Number Examined	54 ^b	10	10	10	10	11	10	10
Hyperplasia, Spindle Cell	24	3	3	4	1	5	3	6
Regression, X-zone								1
<u>CERVIX^c</u>								
Number Examined	55	10	10	10	10	11	12	12
No Findings								
<u>CLITORAL GLAND^d</u>								
Number Examined							1	
Abscess							1	
<u>INTESTINE-LARGE, COLON^d</u>								
Number Examined						1		
No Findings								
<u>KIDNEY</u>								
Number Examined	55	10	10	10	10	11	11	10
Calculus, Pelvis	1							
Cyst, Cortex	5		1	2	2	1	1	1
Dilatation, Tubule, Papillae				1				
Ectopic Adrenal Gland	1							
Hydronephrosis, Unilateral	1						2	
Infiltrative Cell, Mononuclear Cell	8	1	1	3	2	3	1	
Inflammation, Chronic	2						1	
Inflammation, Tubulointerstitial, Medulla	3		1		3		1	
Mineralization, Corticomedullary Junction						1	2	
Mineralization, Papillae	6				1	1	1	1
Necrosis, Renal Tubule, Cortex						1		
Nephropathy	10	1	3		1	1	4	1

Table 51. Summary of the F₁ Female Macroscopic and Microscopic Necropsy Findings (page 4 of 5)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed) ^{0.3 5 50 600}							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
LIVER								
Number Examined	55	10	10	10	10	11	10	10
Hypertrophy, Hepatocyte, Centrilobular	2					3	7	
Infiltrative Cell, Mononuclear Cell	3				2			2
Necrosis, Hepatocyte, Focal	3				1	1		1
Polycystic, Bile Duct				1				
MAMMARY								
Number Examined	55	10	10	10	10	11	10	10
Inflammation, Dermis, Subacute	1		2					1
OVARY^c								
Number Examined	55	11	11	10	10	11	15	18
Cyst, Bursal							2	
Cyst, Follicle	2							
Cyst, Paraovarian	14	1	1	1	2	2	7	9
Cyst, Paraovarian, Bilateral							2	1
PITUITARY								
Number Examined	54 ^b	10	10	10	g ^b	11	g ^b	g ^b
No Findings								
SKIN^d								
Number Examined	1			1			1	2
Ulcer, Epithelium								1
SKIN, NOSE^d								
Number Examined							1	
No Findings								

Table 51. Summary of the F₁ Female Macroscopic and Microscopic Necropsy Findings (page 5 of 5)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>SPLEEN</u>								
Number Examined	55	10	10	10	10	11	10	10
Angiectasis						1		
Depletion, Lymphocyte		1						
Hematopoietic Cell Proliferation	2			1		1	1	2
<u>THYROID</u>								
Number Examined	53 ^b	10	10	10	10	11	10	10
Cyst, Follicle				1			1	
Ectopic Thymus	5				1	1	1	
Infiltrative Cell, Mononuclear Cell	2							
<u>UTERINE HORN^c</u>								
Number Examined	55	11	10	10	11	12	11	13
Cyst, Endometrium	3	1				1	1	1
Decidual Reaction					1			
Dilatation, Lumen, Bilateral	1	1						2
Dilatation, Lumen, Unilateral								1
Inflammation, Acute						1		
<u>VAGINA^c</u>								
Number Examined	55	10	10	10	10	11	11	11
Cyst		1						

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^bThere was not a section of this tissue available for evaluation for one or more females.

^cIncludes females with suspected reduced fertility.

^dIncludes only those females with a macroscopic necropsy finding for this tissue.

Table 53. Summary and Statistical Analysis of the F₁ Retained Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. of F ₁ Retained Males Evaluated	50	27	22	25	26	21	22 ^b	19
Day of Preputial Separation ^c #	26.6 ††† ± 0.2 N=50	26.3 ± 0.3 N=27	26.3 ± 0.6 N=22	25.9 † ± 0.2 N=25	25.9 ± 0.3 N=26	26.5 ± 0.3 N=21	28.3 ††† ± 0.5 N=22	33.3 †††† ± 1.1 N=19
Body Weight (g) on Day of Acquisition ^c #	18.07 ††† ± 0.27 N=50	18.62 ± 0.51 N=27	17.42 ± 0.29 N=22	17.98 ± 0.41 N=25	17.80 ± 0.38 N=26	18.39 ± 0.46 N=21	17.81 ± 0.36 N=22	22.33 †††† ± 0.70 N=19
Adjusted Day of Preputial Separation ^d	26.6 ††† ± 0.2 N=50	26.2 ± 0.3 N=27	26.5 ± 0.5 N=22	26.0 † ± 0.3 N=25	26.0 ± 0.3 N=26	26.5 ± 0.3 N=21	28.4 ††† ± 0.5 N=22	32.6 †††† ± 1.0 N=19
Body Weight (g) on Postnatal Day 30 ^c	23.02 ††† ± 0.44 N=49 ^e	24.02 ± 0.56 N=27	22.89 ± 0.84 N=22	23.74 ± 0.62 N=25	23.52 ± 0.57 N=26	23.80 ± 0.53 N=21	20.60 * ± 0.82 N=22	20.59 * ± 0.68 N=19
Adjusted Day of Preputial Separation ^f	26.6 ††† ± 0.1 N=49 ^e	26.8 ± 0.3 N=27	26.3 ± 0.2 N=22	26.3 ± 0.2 N=25	26.2 ± 0.2 N=26	26.9 ± 0.2 N=21	27.3 † ± 0.3 N=22	32.3 †††† ± 0.9 N=19

Table 53. Summary and Statistical Analysis of the F₁ Retained Male Preputial Separation Data (page 2 of 2)

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups

^bMale 2191 was euthanized moribund on study day -11 (postnatal day 22).

^cReported as the mean \pm S.E.M with day being postnatal day.

^dReported as the adjusted mean (body weight at acquisition as covariate) \pm S.E.M

^eDecrease in N is due to one body weight inadvertently not being recorded on postnatal day 30.

^fReported as the adjusted mean (body weight on postnatal day 30 as covariate) \pm S.E.M

[#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects

††† $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.

‡ $p < 0.05$; Individual t-test for pairwise comparisons to control in robust regression model.

‡‡ $p < 0.01$, Individual t-test for pairwise comparisons to control in robust regression model.

‡‡‡ $p < 0.001$, Individual t-test for pairwise comparisons to control in robust regression model.

††† $p < 0.001$; ANOVA Test.

* $p < 0.05$, Dunnett's Test

ΣΣΣ $p < 0.001$; Wald Chi-square Test for overall treatment effect in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate

σ $p < 0.05$, Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate

σσ $p < 0.01$; Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate.

σσσ $p < 0.001$; Individual t-test for pairwise comparisons to control in robust regression model with body weight on day of acquisition or postnatal day 30 as a covariate

Table 57 Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 1 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
No. of F ₁ Retained Males at Scheduled Sacrifice	50	27	22	25	26	21	22 ^b	19
Sacrifice Body Weight (g) ^c	40.46 †† ± 0.67 N=50	41.32 ± 0.83 N=27	41.43 ± 1.12 N=22	41.75 ± 1.02 N=25	40.83 ± 0.91 N=26	41.51 ± 0.82 N=21	36.59 ** ± 0.83 N=22	38.46 ± 0.76 N=19
Brain Weight (g) ^c	0.5148 ± 0.0042 N=48 ^d	0.5071 ± 0.0065 N=27	0.5159 ± 0.0073 N=22	0.5234 ± 0.0067 N=25	0.5121 ± 0.0077 N=25 ^d	0.5230 ± 0.0070 N=21	0.5083 ± 0.0070 N=22	0.5063 ± 0.0062 N=17 ^d
Pituitary Weight (g) ^c	0.0025 † ± 0.0000 N=47 ^{e,f}	0.0026 ± 0.0001 N=27	0.0027 ± 0.0001 N=21 ^e	0.0027 ± 0.0001 N=24 ^e	0.0027 ± 0.0001 N=25 ^e	0.0028 ** ± 0.0001 N=21	0.0027 ± 0.0001 N=22	0.0028 * ± 0.0001 N=19
Thyroid Weight (g) ^c	0.0028 ± 0.0001 N=47 ^e	0.0027 ± 0.0001 N=25 ^e	0.0029 ± 0.0001 N=22	0.0029 ± 0.0001 N=24 ^e	0.0026 ± 0.0001 N=25 ^e	0.0027 ± 0.0001 N=18 ^{e,g}	0.0028 ± 0.0001 N=21 ^e	0.0030 ± 0.0001 N=18 ^e
Liver Weight (g) ^c	2.0530 ± 0.0436 N=50	2.0970 ± 0.0471 N=27	2.1887 ± 0.0716 N=22	2.1042 ± 0.0603 N=25	2.0863 ± 0.0651 N=26	2.2113 ± 0.0707 N=21	2.2910 ± 0.0748 N=22	2.1255 ± 0.0583 N=19
Spleen Weight (g) ^c	0.1221 ± 0.0070 N=50	0.1240 ± 0.0133 N=27	0.1158 ± 0.0107 N=22	0.1352 ± 0.0232 N=25	0.1114 ± 0.0062 N=26	0.1094 ± 0.0046 N=21	0.1078 ± 0.0067 N=22	0.1246 ± 0.0114 N=19
Right Kidney Weight (g) ^c	0.3840 † ± 0.0085 N=50	0.3948 ± 0.0109 N=27	0.4139 ± 0.0119 N=22	0.4175 ± 0.0103 N=25	0.4079 ± 0.0127 N=26	0.4164 ± 0.0095 N=21	0.4424 *** ± 0.0166 N=22	0.4151 ± 0.0106 N=19

Table 57. Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 2 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Left Kidney Weight (g) ^c	0.3673 ††† ± 0.0085 N=50	0.3764 ± 0.0107 N=27	0.3948 ± 0.0105 N=22	0.3957 ± 0.0080 N=25	0.3965 ± 0.0122 N=26	0.4166 ** ± 0.0099 N=21	0.4257 *** ± 0.0142 N=22	0.4021 ± 0.0101 N=19
Paired Adrenal Gland Weight (g) ^c	0.0063 ± 0.0003 N=48 ^h	0.0068 ± 0.0004 N=26 ^g	0.0075 ± 0.0006 N=22	0.0074 ± 0.0005 N=25	0.0067 ± 0.0003 N=249, ^h	0.0070 ± 0.0004 N=21	0.0073 ± 0.0005 N=219	0.0074 ± 0.0006 N=19
Paired Testis Weight (g) ^c	0.2557 ‡ ± 0.0056 N=50	0.2459 ± 0.0077 N=27	0.2713 ± 0.0072 N=22	0.2701 ± 0.0080 N=249	0.2428 ± 0.0101 N=26	0.2544 ± 0.0115 N=21	0.2375 ± 0.0074 N=22	0.2427 ± 0.0093 N=19
Paired Epididymis Weight (g) ^c	0.1093 ‡ ± 0.0020 N=50	0.1085 ± 0.0032 N=27	0.1159 ± 0.0025 N=22	0.1146 ± 0.0029 N=25	0.1133 ± 0.0024 N=26	0.1082 ± 0.0028 N=21	0.1017 ± 0.0028 N=22	0.1078 ± 0.0024 N=19
Seminal Vesicles with Coagulating Gland Weight (g) ^c	0.3642 ‡ ± 0.0114 N=50	0.3530 ± 0.0144 N=26 ⁱ	0.3958 ± 0.0201 N=22	0.3778 ± 0.0180 N=25	0.3772 ± 0.0183 N=25 ^j	0.4253 ± 0.0224 N=21	0.3280 ± 0.0193 N=22	0.3640 ± 0.0236 N=19
Ventral Prostate Weight (g) ^c	0.0288 ± 0.0021 N=50	0.0297 ± 0.0021 N=27	0.0318 ± 0.0032 N=22	0.0326 ± 0.0032 N=25	0.0283 ± 0.0027 N=26	0.0321 ± 0.0030 N=20 ^j	0.0208 ± 0.0014 N=219	0.0258 ± 0.0016 N=19
Dorsolateral Prostate Weight (g) ^c	0.0456 ± 0.0022 N=50	0.0469 ± 0.0038 N=27	0.0515 ± 0.0051 N=22	0.0504 ± 0.0033 N=25	0.0461 ± 0.0035 N=26	0.0391 ± 0.0037 N=20 ^g	0.0422 ± 0.0032 N=22	0.0517 ± 0.0049 N=19

Table 57. Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 3 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol
	0 ^a	0.018	0.18	1.8	30	300	3500	(ppm in the feed)
Prostate Weight (g) ^C	0.0744 ± 0.0029 N=50	0.0766 ± 0.0037 N=27	0.0832 ± 0.0061 N=22	0.0830 ± 0.0048 N=25	0.0744 ± 0.0041 N=26	0.0712 ± 0.0047 N=20 ^k	0.0626 ± 0.0037 N=21 ^k	0.0774 ± 0.0053 N=19
Relative Brain Weight (% of sacrifice weight) ^C	1.2900 †† ± 0.0203 N=48 ^d	1.2371 ± 0.0233 N=27	1.2635 ± 0.0368 N=22	1.2684 ± 0.0295 N=25	1.2659 ± 0.0286 N=25 ^d	1.2704 ± 0.0316 N=21	1.4001 * ± 0.0284 N=22	1.3106 ± 0.0278 N=17 ^d
Relative Pituitary Weight (% of sacrifice weight) ^C	0.0063 ††† ± 0.0001 N=47 ^{e,f}	0.0062 ± 0.0001 N=27	0.0066 ± 0.0002 N=21 ^e	0.0066 ± 0.0002 N=24 ^e	0.0067 ± 0.0002 N=25 ^e	0.0068 ± 0.0002 N=21	0.0073 *** ± 0.0002 N=22	0.0073 *** ± 0.0002 N=19
Relative Thyroid Weight (% of sacrifice weight) ^C	0.0070 †† ± 0.0002 N=47 ^e	0.0065 ± 0.0003 N=25 ^e	0.0071 ± 0.0004 N=22	0.0070 ± 0.0002 N=24 ^e	0.0063 ± 0.0003 N=25 ^e	0.0066 ± 0.0002 N=18 ^{e,g}	0.0077 ± 0.0003 N=21 ^e	0.0078 ± 0.0003 N=18 ^e
Relative Liver Weight (% of sacrifice weight) ^C	5.0807 ††† ± 0.0735 N=50	5.0978 ± 0.1072 N=27	5.2912 ± 0.1107 N=22	5.0705 ± 0.1381 N=25	5.1021 ± 0.0909 N=26	5.3157 ± 0.1091 N=21	6.2526 *** ± 0.1285 N=22	5.5216 * ± 0.0952 N=19
Relative Spleen Weight (% of sacrifice weight) ^C	0.3069 ± 0.0210 N=50	0.3123 ± 0.0460 N=27	0.2872 ± 0.0341 N=22	0.3332 ± 0.0644 N=25	0.2730 ± 0.0139 N=26	0.2645 ± 0.0109 N=21	0.2954 ± 0.0172 N=22	0.3253 ± 0.0305 N=19
Relative Right Kidney Weight (% of sacrifice weight) ^C	0.9529 ††† ± 0.0181 N=50	0.9580 ± 0.0199 N=27	1.0059 ± 0.0275 N=22	1.0092 ± 0.0286 N=25	1.0008 ± 0.0241 N=26	1.0087 ± 0.0264 N=21	1.2072 *** ± 0.0337 N=22	1.0848 ** ± 0.0308 N=19

Table 57. Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 4 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Left Kidney Weight (% of sacrifice weight) ^c	0.9116 ††† ± 0.0189 N=50	0.9108 ± 0.0192 N=27	0.9599 ± 0.0251 N=22	0.9564 ± 0.0228 N=25	0.9736 ± 0.0239 N=26	1.0090 * ± 0.0269 N=21	1.1632 *** ± 0.0303 N=22	1.0497 *** ± 0.0272 N=19
Relative Paired Adrenal Gland Weight (% of sacrifice weight) ^c	0.0160 ± 0.0008 N=48 ^h	0.0166 ± 0.0011 N=26 ^g	0.0185 ± 0.0017 N=22	0.0179 ± 0.0014 N=25	0.0166 ± 0.0009 N=249 ^h	0.0170 ± 0.0011 N=21	0.0204 ± 0.0014 N=219	0.0195 ± 0.0015 N=19
Relative Paired Testis Weight (% of sacrifice weight) ^c	0.6393 ± 0.0155 N=50	0.5993 ± 0.0195 N=27	0.6623 ± 0.0212 N=22	0.6488 ± 0.0224 N=24 ^g	0.6036 ± 0.0278 N=26	0.6163 ± 0.0295 N=21	0.6549 ± 0.0232 N=22	0.6337 ± 0.0251 N=19
Relative Paired Epididymis Weight (% of sacrifice weight) ^c	0.2722 ± 0.0050 N=50	0.2637 ± 0.0071 N=27	0.2829 ± 0.0080 N=22	0.2770 ± 0.0074 N=25	0.2790 ± 0.0055 N=26	0.2626 ± 0.0081 N=21	0.2795 ± 0.0079 N=22	0.2825 ± 0.0088 N=19
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight) ^c	0.9019 ± 0.0262 N=50	0.8579 ± 0.0326 N=26 ⁱ	0.9546 ± 0.0389 N=22	0.9100 ± 0.0422 N=25	0.9309 ± 0.0402 N=25 ⁱ	1.0209 ± 0.0483 N=21	0.8946 ± 0.0468 N=22	0.9439 ± 0.0553 N=19
Relative Ventral Prostate Weight (% of sacrifice weight) ^c	0.0715 ± 0.0052 N=50	0.0716 ± 0.0047 N=27	0.0763 ± 0.0074 N=22	0.0794 ± 0.0081 N=25	0.0698 ± 0.0066 N=26	0.0764 ± 0.0061 N=20 ^j	0.0572 ± 0.0039 N=21 ^g	0.0676 ± 0.0044 N=19
Relative Dorsolateral Prostate Weight (% of sacrifice weight) ^c	0.1131 ± 0.0053 N=50	0.1144 ± 0.0093 N=27	0.1247 ± 0.0120 N=22	0.1212 ± 0.0075 N=25	0.1116 ± 0.0073 N=26	0.0951 ± 0.0095 N=20 ^g	0.1158 ± 0.0089 N=22	0.1346 ± 0.0129 N=19

Table 57 Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 5 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Prostate Weight (% of sacrifice weight) ^C	0.1846 ± 0.0071 N=50	0.1859 ± 0.0086 N=27	0.2010 ± 0.0132 N=22	0.2006 ± 0.0118 N=25	0.1814 ± 0.0085 N=26	0.1715 ± 0.0104 N=20 ^k	0.1720 ± 0.0104 N=21 ^k	0.2022 ± 0.0136 N=19
Relative Pituitary Weight (% of brain weight) ^C	0.4908 ‡ ± 0.0089 N=45 ^{d,e,f}	0.5087 ± 0.0143 N=27	0.5237 ± 0.0162 N=21 ^e	0.5275 ± 0.0157 N=24 ^e	0.5312 ± 0.0159 N=25 ^{d,e}	0.5414 ± 0.0127 N=21	0.5299 ± 0.0187 N=22	0.5596 ** ± 0.0185 N=17 ^d
Relative Thyroid Weight (% of brain weight) ^C #	0.5419 ± 0.0173 N=46 ^{d,e}	0.5350 ± 0.0288 N=25 ^e	0.5649 ± 0.0259 N=22	0.5542 ± 0.0177 N=24 ^e	0.5056 ± 0.0175 N=24 ^{d,e}	0.5198 ± 0.0193 N=18 ^{e,g}	0.5483 ± 0.0187 N=21 ^e	0.5876 ± 0.0248 N=16 ^{d,e}
Relative Liver Weight (% of brain weight) ^C	398.1025 ‡ ± 8.3420 N=48 ^d	414.6543 ± 9.6495 N=27	425.5046 ± 14.6768 N=22	401.8680 ± 9.8523 N=25	409.5556 ± 11.5515 N=25 ^d	424.3139 ± 14.8620 N=21	450.8215 ** ± 13.5519 N=22	422.7625 ± 11.6733 N=17 ^d
Relative Spleen Weight (% of brain weight) ^C	23.8462 ± 1.4282 N=48 ^d	24.8374 ± 2.9992 N=27	22.5881 ± 2.1263 N=22	25.6511 ± 4.1851 N=25	22.0324 ± 1.3630 N=25 ^d	20.9385 ± 0.8332 N=21	21.2753 ± 1.3097 N=22	25.2587 ± 2.4268 N=17 ^d
Relative Right Kidney Weight (% of brain weight) ^C	74.6257 ‡‡ ± 1.5638 N=48 ^d	77.9899 ± 2.1762 N=27	80.6087 ± 2.6541 N=22	79.8336 ± 1.8411 N=25	80.0457 ± 2.0949 N=25 ^d	79.9456 ± 2.1715 N=21	86.9966 *** ± 2.8928 N=22	83.3452 * ± 2.0282 N=17 ^d
Relative Left Kidney Weight (% of brain weight) ^C	71.0948 ‡‡‡ ± 1.6216 N=48 ^d	74.3140 ± 2.0973 N=27	76.9958 ± 2.5454 N=22	75.7301 ± 1.5138 N=25	77.8977 ± 2.0194 N=25 ^d	79.8221 * ± 1.9348 N=21	83.7712 *** ± 2.5371 N=22	80.2766 * ± 1.8734 N=17 ^d

Table 57. Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 6 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Relative Paired Adrenal Gland Weight (% of brain weight) ^c	1.2545 ± 0.0580 N=46 ^{d,h}	1.3532 ± 0.0933 N=26 ^g	1.4454 ± 0.1021 N=22	1.4113 ± 0.1041 N=25	1.3220 ± 0.0641 N=23 ^{d,g,h}	1.3312 ± 0.0693 N=21	1.4472 ± 0.0955 N=21 ^g	1.5004 ± 0.1135 N=17 ^d
Relative Paired Testis Weight (% of brain weight) ^c	49.5257 ± 1.0253 N=48 ^d	48.6343 ± 1.5544 N=27	52.7289 ± 1.4465 N=22	51.6508 ± 1.6504 N=24 ^g	47.2391 ± 2.0399 N=25 ^d	48.9131 ± 2.3595 N=21	46.8081 ± 1.4307 N=22	48.1145 ± 2.2090 N=17 ^d
Relative Paired Epididymis Weight (% of brain weight) ^c	21.2974 ‡ ± 0.3231 N=48 ^d	21.4247 ± 0.5981 N=27	22.5565 ± 0.5819 N=22	21.9358 ± 0.5411 N=25	22.1999 ± 0.4615 N=25 ^d	20.7725 ± 0.5997 N=21	19.9884 ± 0.4300 N=22	21.4117 ± 0.5994 N=17 ^d
Relative Seminal Vesicles with Coagulating Gland Weight (% of brain weight) ^c	70.5034 ± 2.2433 N=48 ^d	69.8447 ± 2.9351 N=26 ⁱ	77.1121 ± 4.0945 N=22	72.3151 ± 3.3884 N=25	74.2723 ± 3.4366 N=24 ^{d,i}	81.4511 ± 4.2618 N=21	64.4454 ± 3.5847 N=22	73.1717 ± 5.1059 N=17 ^d
Relative Ventral Prostate Weight (% of brain weight) ^c	5.3697 ± 0.3566 N=48 ^d	5.8765 ± 0.4301 N=27	6.1298 ± 0.6060 N=22	6.1825 ± 0.5757 N=25	5.4387 ± 0.5045 N=25 ^d	6.1642 ± 0.6000 N=20 ^j	4.1163 ± 0.2960 N=21 ^g	5.0320 ± 0.3471 N=17 ^d
Relative Dorsolateral Prostate Weight (% of brain weight) ^c #	8.8365 ± 0.4317 N=48 ^d	9.2512 ± 0.7419 N=27	10.0480 ± 1.0038 N=22	9.6928 ± 0.6565 N=25	9.0616 ± 0.6755 N=25 ^d	7.5185 ± 0.7222 N=20 ^g	8.2841 ± 0.5869 N=22	10.9576 ± 1.0573 N=17 ^d
Relative Prostate Weight (% of brain weight) ^c	14.2063 ‡ ± 0.5360 N=48 ^d	15.1277 ± 0.7351 N=27	16.1776 ± 1.1919 N=22	15.8753 ± 0.8979 N=25	14.5002 ± 0.7170 N=25 ^d	13.6827 ± 0.9439 N=20 ^k	12.3246 ± 0.6996 N=21 ^k	15.9896 ± 1.2047 N=17 ^d

Table 57 Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 7 of 8)

	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Percent Motile Sperm ^c	49.8 ± 1.3 N=50	47.7 ± 1.9 N=27	44.7 ± 2.3 N=22	46.8 ± 1.8 N=25	48.7 ± 2.0 N=26	50.0 ± 2.0 N=21	48.8 ± 1.8 N=21 ^l	47.3 ± 2.2 N=19
Percent Progressively Motile Sperm ^c	44.9 ± 1.2 N=50	42.2 ± 1.9 N=27	38.0 ± 2.5 N=22	40.9 ± 1.9 N=25	43.9 ± 1.9 N=26	45.4 ± 1.6 N=21	45.0 ± 1.6 N=21 ^l	44.2 ± 2.1 N=19
Epididymal Sperm Concentration (10 ⁶ /g) ^c	1791.18 ± 48.51 N=50	1766.07 ± 80.50 N=27	1768.51 ± 92.41 N=22	1787.55 ± 63.87 N=25	1690.79 ± 85.11 N=26	1712.34 ± 104.60 N=21	1600.76 ± 84.80 N=21 ^l	1676.63 ± 76.41 N=19
Spermatid Head Concentration (10 ⁶ /g) ^c	250.65 ± 12.28 N=50	252.93 ± 16.00 N=27	241.64 ± 14.58 N=22	242.30 ± 17.42 N=25	256.38 ± 15.03 N=26	236.02 ± 16.08 N=21	227.90 ± 16.75 N=22	246.83 ± 13.23 N=19
Daily Sperm Production per Testis (10 ⁶ /testis/day) ^c	7.07 ± 0.40 N=50	6.83 ± 0.48 N=27	7.09 ± 0.57 N=22	7.07 ± 0.54 N=25	7.19 ± 0.49 N=26	6.82 ± 0.54 N=21	5.95 ± 0.55 N=22	6.51 ± 0.34 N=19
Efficiency of Daily Sperm Production (10 ⁶ /g. testis/day) ^c	51.79 ± 2.54 N=50	52.26 ± 3.31 N=27	49.93 ± 3.01 N=22	50.06 ± 3.60 N=25	52.97 ± 3.11 N=26	48.76 ± 3.32 N=21	47.09 ± 3.46 N=22	51.00 ± 2.73 N=19
Percent Abnormal Sperm ^c	2.25 ± 0.10 N=50	1.93 ± 0.10 N=27	2.23 ± 0.15 N=21 ^m	2.15 ± 0.14 N=25	2.06 ± 0.11 N=26	1.99 ± 0.14 N=21	2.30 ± 0.15 N=21 ^l	2.11 ± 0.17 N=19

Table 57. Summary and Statistical Analysis of the F₁ Retained Male Organ Weights, Relative Organ Weights and Andrology Assessment (page 8 of 8)

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2). See Appendix III for the comparison of the two control groups.

^bMale 2191 was found dead on study day -11 (study day 0 was first day of the formal postwean holding period and negative study days were during the holding period prior to the start of the formal postwean holding period)

^cReported as the mean \pm S.E.M.

^dDecrease in N is due to not all of the brain tissue being present at time of weighing for one or more animals.

^eDecrease in N is due to part or all of one or more organs not being present in the tissue cup at the time of weighing the fixed organ.

^fDecrease in N is due to one pituitary disintegrating when it was removed for fixed weighing.

^gDecrease in N is due to one weight being a statistical outlier and, therefore, it was excluded.

^hDecrease in N is due to one of the adrenal glands being lost prior to weighing for one or more animals and, therefore the paired adrenal gland weight could not be obtained.

ⁱDecrease in N is due to one pair of seminal vesicles being nicked prior to weighing and, therefore, an accurate weight could not be obtained.

^jDecrease in N is due to the ventral prostate from one animal being lost prior to weighing.

^kDecrease in N is due to either the ventral or dorsolateral prostate weight being missing and, therefore, the total prostate weight could not be calculated

^lDecrease in N is due to the epididymides being placed in formalin therefore, no motility or morphology or epididymal concentration analysis could be performed.

^mDecrease in N is due to the epididymal sperm suspension spilling prior to the morphology slides being made and, therefore, no morphology analysis could be performed.

[#]Levene's test for homogeneity of variances was significant ($p < 0.05$), therefore robust regression methods were used to test all treatment effects

[†] $p < 0.05$; ANOVA Test

^{††} $p < 0.01$, ANOVA Test.

^{†††} $p < 0.001$; ANOVA Test.

^{*} $p < 0.05$; Dunnett's Test.

^{**} $p < 0.01$; Dunnett's Test

^{***} $p < 0.001$, Dunnett's Test.

Table 58. Summary of the F₁ Retained Male Macroscopic and Microscopic Necropsy Findings (page 1 of 4)

MACROSCOPIC FINDINGS

SCHEDULED NECROPSY:

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
Alopecia:	1							
neck							1	
nose			1		2	1		
Ear(s): severely damaged from the feed jar	1							
Eye(s): abscess below, left		1						
Kidney: hydronephrosis, bilateral	1	1				1	1	1
hydronephrosis, left						1		1
hydronephrosis, right		1		1		1	1	1
Liver: pale	1							
Penis: hard mass attached								1
Preputial Gland: enlarged, right	1							
Prostate, Dorsal: reduced in size						1	1	
Prostate, Ventral: reduced in size					1		1	
Seminal Vesicle: atrophied, left								1
reduced in size, left	1				1			1
reduced in size, right								1
Sore(s): ear, bilateral	1							
ears, neck and left of penis								1
ears, neck and right side of abdomen			1					
neck	1	1					1	
under neck				1				
Spleen: enlarged	2	1	1	1			1	1
Testis: undescended, bilateral		1						
Thin fur: hip, left		1						
multiple areas					1			

Table 58. Summary of the F₁ Retained Male Macroscopic and Microscopic Necropsy Findings (page 2 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
<u>ADRENAL GLAND</u>								
Number Examined	50	10	10	10	10	10	10	10
Hyperplasia, Spindle Cell	4	1					2	1
Vacuolization, Cytoplasmic, Cortex	1							
<u>COAGULATING GLAND</u>								
Number Examined	50	10	10	10	10	10	10	10
No Findings								
<u>EPIDIDYMIS</u>								
Number Examined	49 ^b	10	10	10	10	10	10	10
Degeneration, Epithelium, Tubule						1		
Exfoliated Germ Cells		1						
Infiltrative Cell, Mononuclear Cell	1					1	1	
<u>KIDNEY</u>								
Number Examined	50	10	10	10	10	10	10	10
Cyst, Cortex	7					1		
Hydronephrosis, Bilateral	2			1		2	2	1
Hydronephrosis, Unilateral	1	1	1		1	1		4
Infiltrative Cell, Mononuclear Cell	2	2	2	2	2	1		1
Inflammation, Acute							1	
Inflammation, Chronic	2						1	
Inflammation, Tubulointerstitial, Medulla		2	2	1	2	1		
Mineralization, Corticomedullary Junction	1		1					
Mineralization, Papillae	1	1	1					
Nephropathy	8	1			2		3	1

Table 58 Summary of the F₁ Retained Male Macroscopic and Microscopic Necropsy Findings (page 3 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
LIVER								
Number Examined	50	10	10	10	10	10	10	10
Hypertrophy, Hepatocyte, Centriobular Infiltrative Cell, Mononuclear Cell	4	1	3	2	2	5	7	
Necrosis, Hepatocyte, Focal	1	1		1			1	
Vacuolar Degeneration, Hepatocyte, Centriobular	5				1	1		
PITUITARY								
Number Examined	47 ^b	10	10	10	10	10	10	10
Cyst, Pars Distalis	1							
PREPUTIAL GLAND^c								
Number Examined								1
Abscess								1
PROSTATE, DORSOLATERAL								
Number Examined	49 ^b	10	10	10	10	10	g ^b	10
Infiltrative Cell, Mononuclear Cell					1			
Inflammation, Chronic	1							
Necrosis, Epithelial							1	
PROSTATE, VENTRAL								
Number Examined	46 ^b	10	g ^b	g ^b	10	10	g ^b	g ^b
Infiltrative Cell, Mononuclear Cell	4		2					
SEMINAL VESICLES								
Number Examined	50	10	10	10	10	10	10	10
No Findings								
SKIN^c								
Number Examined	2	1	1	1	2		1	
Hyperplasia, Epithelium		1						
Ulcer, Epithelium	2		1	1			1	

Table 58. Summary of the F₁ Retained Male Macroscopic and Microscopic Necropsy Findings (page 4 of 4)

MICROSCOPIC FINDINGS

Finding	Bisphenol A (ppm in the feed)							17β-Estradiol (ppm in the feed)
	0 ^a	0.018	0.18	1.8	30	300	3500	0.5
SPLEEN								
Number Examined	50	10	10	10	10	10	10	10
Hematopoietic Cell Proliferation	5	2	1	1			4	1
Hyperplasia, Lymphoid	1							
TESTIS								
Number Examined	50	10	10	10	10	10	10	10
Degeneration, Seminiferous Tubule	2	1		1	1		2	
THYROID								
Number Examined	50	g ^b	10	10	10	10	10	10
Cyst, Follicle	1							
Ectopic Thymus	4	2	2	1			2	2
Infiltrative Cell, Mononuclear Cell				1				

^aCombined 0 ppm Bisphenol A groups (control group 1 and control group 2).

^bThere was not a section of this tissue available for evaluation for one or more males

^cIncludes only those males with a macroscopic necropsy finding for this tissue

$$\frac{5}{50} = 10\%$$

$$\frac{4}{10} = 40\%$$

$$50 \overline{) 500} \begin{array}{r} 10 \\ \underline{50} \\ 0 \end{array}$$

$$\frac{2}{50} = 4\%$$

$$\frac{2}{10} = 20\%$$

$$50 \overline{) 200} \begin{array}{r} 4 \\ \underline{200} \\ 0 \end{array}$$