DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

AD

Date July 18, 2007

From Yan Gu, Ph D
Toxicology Group II, Division of Food Contact Notifications (DFCN)

Subject Review of study entitled "Three-Generation Reproductive Toxicity Evaluation of Bisphenol A in the Feed to CD® (Sprague-Dawley) Rats"

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

1. Introduction

A three-generation reproductive toxicity study, one litter per generation, with dietary bisphenol A (BPA) was conducted in CD Sprague-Dawley rats. The objectives of this study were to evaluate the potential of BPA, administered in the feed to CD® rats, to produce alterations in male or female fertility, pregnancy and lactation, and growth and development of the offspring for three generations. The study was also designed to evaluate the concerns for possible low-dose effects and for possible effects of exposure to BPA during sensitive life stages over three generations of offspring using an internationally accepted reproductive toxicity protocol under Good Laboratory Practice (GLP) regulation (U S. EPA, 1989)

The dietary bisphenol A (CAS No. 80-05-7, 99.5% purity) of 0, 0.015, 0.3, 4.5, 75, 750, and 7500 ppm (equivalent to estimated daily intake of 0, 0.001, 0.02, 0.3, 5, 50, and 500 mg/kg bw/day) was administered to CD-SD virgin rats (30 animals/sex/dose) in the diet *at libitum* for 10-week prebreed exposure period, during mating, during gestation, and females through lactation until weaning. All F0 males were sacrificed and necropsied after F1 delivery. F1 litters were culled to 10 pups (equal sex ratio, if possible) on postnatal day (PND) 4. At weaning (PND 21), 30/sex/dose were randomly selected as F1 parents. Selected F1 weanlings were administered BPA in the diet for the similar exposure periods (13-15 weeks for prebreed period) as described for F0 generation and so were F2 weanlings. F3 weanlings were held for approximately 10 weeks with continuing dietary exposure The dose range in this study has covered, particularly at the lower end, the doses at which significant oral low-dose toxicity in male rodents has been previously reported.

The study was performed by following the U.S. EPA OPPTS test guidelines with additional assessments, such as a third offspring generation, one control and 6 dosing groups, test for retained nipples and areolae in male F1, F2, and F3 preweanlings, and retention of F3 offspring until adulthood with continuing exposure, with histopathologic and andrological assessments at their termination. A number of parental systemic, reproductive and offspring parameters were measured in this study. Briefly, these parameters included: mortality, clinical observations, body weights, body weight changes, feed consumption, organ weights (absolute and relative, general and reproductive; including liver, paired kidneys, adrenal glands, spleen, brain, pituitary, paired ovaries, uterus, testes, epididymides, prostate, preputial gland, seminal vesicles with coagulating glands, etc.), gross necropsy, histopathology (liver, kidneys, spleen, pituitary gland, adrenal glands, urinary bladder, coagulating glands, preputial gland, prostate, seminal vesicles, testis, cervix, vagina, uterus with oviducts, etc.), vaginal cyclicity, estrous cycle length, mating, fertility, pregnancy and gestational indices, PND survival, postimplantation loss, stillbirth, live birth, lactation indices, number of implantation sites, total, live and dead pups per litter, sex ratio, daily spermatid production (DSP), efficiency of DSP, percent of abnormal and motile sperms, acquisition of preputial separation (PPS) and vaginal patency (VP), anogenital distance (AGD), etc.

Several types of statistical analyses were performed in the study depending on the data, i.e. quantitative continuous, frequency, covariance, or correlated data.

A comprehensive summary of this study has been published, entitled "Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats"[1], which is attached. Therefore, a full length study report review was not performed by this reviewer Only those reported pivotal and/or questionable findings reported in the article or the summary of the study report were examined and compared with the available study data submitted in Agency's original file

2. Results

Parental Systemic

No statistically or biologically significant, treatment-related mortality was observed across all groups in any generations (Text Table E; *Tables 32, 63, 94*)[2].

Consistent and persistent reductions in body weights and body weight gains were evident for F0, F1, F2, and F3 generations in both sexes (Text Table E; Tables 3, 6, 22, 34, 37, 53, 65, 68, 84, 96, 99). Body weights were significantly reduced during gestation and lactation in F0, F1 and F2 females at 7500 ppm, during gestation and lactation in F0 and F2 females and during lactation in F1 females at 750 ppm (Tables 10, 13, 41, 44, 72, 75). Terminal body weights at necropsy were significantly decreased for both sexes in all generations at 7500 ppm, in F1 females at 750 ppm and in F1 and F2 males at 750 ppm (Tables 28, 30, 59, 61, 90, 92, 103, 105).

Feed consumption was variable among treated groups during different periods in the study. However, no treatment-related effects were observed. The feed consumption reached highest levels in the prebreed and lactation periods; consequently, so was the intake of BPA (*Tables 4, 7, 11, 14, 23, 26, 35, 38, 42, 45, 54, 57, 66, 69, 73, 76, 85, 88, 97, 100*).

No treatment-related clinical observations were reported across all groups in any generations during the study (*Tables 5, 8, 12, 15, 18, 24, 27, 36, 39, 43, 46, 49, 55, 58, 67, 70, 74, 77, 80, 86, 89, 98, 101*).

At necropsy, most measured organ weights were reduced for F0, F1, F2 parental animals and F3 retained adults at 7500 ppm. On the other hand, relative organ weights were significantly increased (or unchanged) at 7500 ppm, such as liver, kidney, adrenal glands, and brain (Tables 28, 30, 59, 61, 90, 92, 103, 105). These effects were attributed to reduced terminal

---

[1] RW Tyl et al.: Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats. Toxicological Sciences 68 121-146, 2002,

[2] The tables with italic numbers are not attached with this memo

body weights. Changes of absolute and relative organ weights occurred occasionally, such as pituitary and spleen, but they were not dose-related or not consistent across generations.

No treatment-related gross or histopathological findings were reported for the examined organs for F0, F1, F2 parental animals and F3 retained adults for either sex, except for slight to mild renal tubular degeneration and chronic hepatic inflammation observed at a higher incidence in F1 and F2 females, and chronic hepatic inflammation in F0 males at 7500 ppm (*Tables 29, 31, 60, 62, 91, 93, 104, 106*).

Parental Reproductive

Except for significantly reduced absolute and relative paired ovarian weights (Tables 30, 61, 92), same trends of decrease in absolute organ weights and increase in relative organ weights were also observed in reproductive organ weights in both sexes across all groups for all generations (Tables 28, 30, 59, 61, 90, 92). Again, they were attributed to reduced terminal body weights.

Absolute paired ovarian weights were significantly reduced in F0, F1, F2, and F3 females. In addition, relative paired ovarian weights were also significantly reduced in F0, F1 and F2 females at 7500 ppm in the presence of significant systemic maternal toxicity (reduced body and organ weights) (Tables 30, 61, 92).

For parental females, there were no treatment-related effects on mating, fertility, pregnancy, or gestational indices, dead pups per litter, or postimplantation (prenatal) loss in F0, F1, and F2 females (Tables 16, 47, 78). There were no changes in estrous cycle length in any groups for F0, F1, F2, and F3 females (*Tables 9, 40, 71, 102*). Paired ovarian primordial follicle counts were not significantly different between high dose and control in F1, F2, and F3 females, but an increase at 7500 ppm for F0 females was reported (Tables 30, 61, 92). No changes were observed for precoital interval or gestational length across all groups for all generations (Tables 16, 47, 78).

Significant reduction in number of implants, total and live pups per litter at birth (PND 0) were observed at 7500 ppm for F1, F2, and F3 offspring (also at 0.3 ppm for F3 offspring)(Tables 16, 47, 78).

For parental males, there were no treatment-related effects on mating or fertility indices (Tables 16, 47, 78). Except for F1 males with a significant reduction, no changes of epididymal sperm concentration were reported in F0, F2, or F3 males at 7500 ppm. Percent motile or progressive motile sperms were not affected across groups in any generations. Testicular homogenization-resistant spermatid head counts, DSP (except for a significant decrease at 7500 ppm for F3 males only), or efficiency of DSP were not changed across groups in any generations of males. Percent abnormal sperm was not affected across all groups in any generations (Tables 28, 59, 90, 103).

No treatment-related gross or histopathological findings in any reproductive organs were observed for F0, F1, F2, or F3 adult males or females in any groups (*Tables 29, 31, 60, 62, 91, 93, 104, 106*).

Offspring

For F1, F2, and F3 offspring, there were no treatment-related changes for stillbirth index, postimplantation loss per litter, sex ratio per litter at birth and throughout lactation, postnatal or lactational or interim offspring survival indices (Tables 17, 48, 79). No statistically significant differences were observed on AGD (F1 offspring was not measured), nipples or areolae per pup or percent of pups with 1 or more nipples per areolae in males (Tables 17, 48, 79).

Pup body weights per litter were significantly decreased at 7500 ppm for F1, F2, and F3 offspring during the lactational period (PND 7, 14, and 21)(Tables 17, 48, 79). Pup body weights were also significantly decreased in F1 at 7500 ppm on PND 4 for all pups analyzed together, but not for sexes analyzed separately (Table 17). All pup body weights per litter were also significantly decreased for F2 offspring at 4.5, 75, and 750 ppm on PND 21 (Table 48).

AGD was significantly increased in F2 females across groups, except for 75 and 7500 ppm (Table 48). The absolute age at vaginal patency (VP) was significantly delayed in F1, F2, and F3 generations at 7500 ppm and F2 generation at 75 ppm When it was adjusted for the body weights, VP was delayed at 7500 ppm for all 3 generations. If it was adjusted for the body weights on SD 7, VP was delayed at 7500 ppm for F1 and F3 generations only (Tables 33, 64, 95).

In males, absolute age at preputial separation (PPS) was significantly delayed in F1 generation at 750 and 7500 ppm, in F2 generation at 0.3, 75, 750 and 7500 ppm, and in F3 generation at 7500 ppm. When it was adjusted for the body weights or for the body weights on SD 14, the age at PPS was delayed in F1 generation at 750 and 7500 ppm and F2 generation at 7500 ppm only (Tables 33, 64, 95).

The absolute organ weights for F1, F2, and F3 weanling offspring sacrificed on PND 21 were mostly decreased and relative organ weights were mostly increased or not changed at 7500 ppm (Tables 20, 51, 82). Again, these effects were attributed to the reduced body weights of weanling offspring.

3. Summary and Conclusions

In summary, adult systemic toxicity of BPA at 750 and 7500 ppm across all generations included: 1) consistently reduced body weights and body weight gains; 2) decreased absolute and increased relative organ weights (weanlings and adults); and 3) slight to mild renal tubular degeneration and/or chronic hepatic inflammation at 7500 ppm. Reported reproductive and offspring toxicity included decreased paired ovarian weights, reduced number of total pups/litter and live pups/litter on PND 0 at 7500 ppm with maternal toxicity, delayed ages at VP and PPS in F1, F2, and F3 offspring at 7500 ppm associated with reduced body weights. Based on reported findings in this study,

The NOEL for systemic toxicity is 75 ppm (5 mg/kg bw/day)

The NOEL for reproductive toxicity is 750 ppm (50 mg/kg bw/day)
The NOEL for offspring (postnatal) toxicity is 750 ppm (50 mg/kg bw/day)

4. Comment

One of the objectives of this study is to "evaluate the concerns for possible low-dose effects" of BPA and no previously reported low-dose effects were observed in this study. This study indeed followed the EPA study guidance. However, it has been recently recommended that for studying endocrine disruptor effects at low dose, the level of phytoestrogens in diets should be minimal. The diet, PMI 5002, used in this study has been characterized as a high phytoestrogen diet[3]. This might reduce the sensitivity of the study for the low-dose effects of BPA

/s/

/s/

Yan Gu

C:\my documents\BPA\Three generation study-memo-final.doc

[3] JE Thigpen et al. Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. ILAR Journal Vol 45 (4).401-416, 2004

Table 3 Summary and Statistical Analysis of th[redacted]Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4.500	75.000	750 000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]							
	226 3 ± 5 5 N=30	228 3 ± 4 8 N=30	225 8 ± 5 1 N=30	226 7 ± 5 5 N=30	226 3 ± 5 5 N=30	224 2 ± 5 4 N=30	227 4 ± 4.8 N=30
Body Weight (sd 7) (g)[a]							
	286 8 ‡‡‡ ± 4 7 §§§ N=30	285.9 ± 4 3 N=30	285 3 ± 4 7 N=30	289 5 ± 4 7 N=30	288.9 ± 4.7 N=30	281.0 ± 4 8 N=30	235.4 *** ± 3 5 N=30
Body Weight (sd 14) (g)[a]							
	328 6 ‡‡‡ ± 4 7 §§§ N=30	324.5 ± 3 8 N=30	326 8 ± 4 6 N=30	324 8 ± 6 7 N=30	323.4 ± 5.5 N=30	318 1 ± 4 2 N=30	264 5 *** ± 3 4 N=30
Body Weight (sd 21) (g)[a]							
	364 0 ‡‡‡ ± 5 0 §§§ N=30	359 7 ± 4 4 N=30	363 2 ± 5 2 N=30	366 2 ± 4 9 N=30	365 2 ± 5 3 N=30	353 7 ± 5 3 N=30	294 0 *** ± 3 6 N=30
Body Weight (sd 28) (g)[a]							
	394 2 ‡‡‡ ± 6 1 §§§ N=30	387 0 ± 5 0 N=30	391 9 ± 6 0 N=30	395 0 ± 4 7 N=30	396 3 ± 5 7 N=30	379 1 ± 6 2 N=30	317 8 *** ± 3 8 N=30
Body Weight (sd 35) (g)[a]							
	421 2 ‡‡‡ ± 6 4 §§§ N=30	413 2 ± 5 5 N=30	416 9 ± 6 4 N=30	423 8 ± 4.9 N=30	423 8 ± 6 0 N=30	402 5 ± 6.7 N=30	342 2 *** ± 4 5 N=30

(continued)

Table 3 Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 42) (g)[a]							
	440 3 ‡‡‡ ± 6 4 §§§ N=30	430 8 ± 5 5 N=30	434.7 ± 6 4 N=30	444 0 ± 5 4 N=30	442.8 ± 6 6 N=30	420 3 ± 7 1 N=30	354 8 *** ± 4 6 N=30
Body Weight (sd 49) (g)[a]							
	461 2 ‡‡‡ ± 6 8 §§§ N=30	450 3 ± 5.9 N=30	454 2 ± 6 8 N=30	464 7 ± 6 0 N=30	463 9 ± 7 1 N=30	439.3 ± 7 7 N=30	366 8 *** ± 5.0 N=30
Body Weight (sd 56) (g)[a]							
	474 3 ‡‡‡ ± 7 0 §§§ N=30	461 9 ± 6 6 N=30	466 1 ± 7 2 N=30	478 2 ± 6.4 N=30	478 7 ± 7 7 N=30	452 0 ± 8 5 N=30	375 8 *** ± 4.8 N=30
Body Weight (sd 63) (g)[a]							
	486 3 ‡‡‡ ± 7 3 §§§ N=30	476 1 ± 6.3 N=29[b]	477 3 ± 7 4 N=30	491 4 ± 6 8 N=30	496 7 ± 7 9 N=30	465 0 ± 8 6 N=30	384 0 *** ± 5.0 N=30
Body Weight (sd 70) (g)[a]							
	502 5 ‡‡‡ ± 7 9 §§§ N=30	489 3 ± 6 6 N=29	492 2 ± 8.0 N=30	505 7 ± 7 1 N=30	508 9 ± 8 9 N=30	480 4 ± 9 5 N=30	401 0 *** ± 5 6 N=30
Body Weight (sd 77) (g)[a]							
	505 0 ‡‡‡ ± 7 4 §§§ N=30	492 3 ± 6 3 N=29	492 2 ± 7 6 N=30	505 4 ± 7 6 N=30	511 9 ± 8 3 N=30	479.4 ± 10 2 N=30	397.1 *** ± 5 2 N=30

(continued)

Table 3 Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Body Weight (sd 84) (g)[a]							
	516 3 ‡‡‡ ± 8 3 §§§ N=30	504.6 ± 6 5 N=29	505 9 ± 7 8 N=30	517 6 ± 7 9 N=30	522 0 ± 9 0 N=30	492.6 ± 9 9 N=30	408 4 *** ± 5 9 N=30
Body Weight Change (sd 0 to 7) (g)[a]							
#	60 5 ¶¶¶ ± 2 3 ¥¥¥ N=30	57 6 ± 1.7 N=30	59 5 ± 2 0 N=30	62 8 ± 1 9 N=30	62.7 ± 2 3 N=30	56 7 ± 2 6 N=30	8.0 ¤¤¤ ± 3.7 N=30
Body Weight Change (sd 7 to 14) (g)[a]							
#	41 8 ¶¶¶ ± 2 4 ¥¥¥ N=30	38.6 ± 1 6 N=30	41 5 ± 2 1 N=30	35 3 ± 5 5 N=30	34 4 ± 4 4 N=30	37 1 ± 1 9 N=30	29.1 ¤¤¤ ± 1.6 N=30
Body Weight Change (sd 14 to 21) (g)[a]							
#	35.4 ¶¶¶ ± 1.6 ¥ N=30	35 2 ± 1 2 N=30	36 4 ± 1 3 N=30	41 4 ± 3.0 N=30	41 8 ± 3.0 N=30	35 6 ± 2 1 N=30	29 6 ¤ ± 2 4 N=30
Body Weight Change (sd 21 to 28) (g)[a]							
	30 2 ‡ ± 1 9 §§ N=30	27 3 ± 1 2 N=30	28.6 ± 1 2 N=30	28.9 ± 1 9 N=30	31 1 ± 1.5 N=30	25 4 ± 1 4 N=30	23 8 * ± 2.0 N=30
Body Weight Change (sd 28 to 35) (g)[a]							
#	27 0 ¶ ± 1.7 N=30	26 2 ± 1.1 N=30	25 0 ± 3 1 N=30	28 7 ± 1.2 N=30	27.5 ± 1 4 N=30	23.4 ¤¤ ± 1 3 N=30	24.3 ± 1 8 N=30

(continued)

Table 3. Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight Change (sd 35 to 42) (g)[a]							
	19 1 ‡‡ ± 0 9 §§§ N=30	17 6 ± 1 1 N=30	17 8 ± 1 5 N=30	20 2 ± 1 4 N=30	19 0 ± 1.2 N=30	17 8 ± 1.1 N=30	12 7 ** ± 1 5 N=30
Body Weight Change (sd 42 to 49) (g)[a]							
	20 9 ‡‡‡ ± 0 9 §§§ N=30	19 6 ± 1 2 N=30	19 6 ± 1 5 N=30	20 7 ± 1 2 N=30	21 1 ± 1 1 N=30	19 0 ± 1 0 N=30	12 0 *** ± 1 7 N=30
Body Weight Change (sd 49 to 56) (g)[a]							
#	13.1 ¶ ± 0.9 N=30	11 6 ± 1 3 N=30	11 9 ± 1 2 N=30	13 5 ± 0 9 N=30	14 8 ± 0.9 N=30	12 6 ± 1 3 N=30	9.0 ¤ ± 2.0 N=30
Body Weight Change (sd 56 to 63) (g)[a]							
#	12 0 ¶¶ ± 0 9 N=30	11 3 ± 0 7 N=29[b]	11 2 ± 0.7 N=30	13.2 ± 0 9 N=30	18.0 ± 3 5 N=30	13 1 ± 0 7 N=30	8 2 ¤ ± 1.5 N=30
Body Weight Change (sd 63 to 70) (g)[a]							
#	16 2 ± 1 5 N=30	13 2 ± 1 9 N=29	14 9 ± 1 2 N=30	14.3 ± 1 1 N=30	12 2 ± 3.8 N=30	15 4 ± 1 6 N=30	17.0 ± 2 5 N=30
Body Weight Change (sd 0 to 70) (g)[a]							
	276 2 ‡‡‡ ± 8 2 §§§ N=30	261 0 ± 6 3 N=29	266 4 ± 8 0 N=30	279 1 ± 8 4 N=30	282 6 ± 8 6 N=30	256 2 ± 9 2 N=30	173.6 *** ± 6.6 N=30

(continued)

Table 3 Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Body Weight Change (sd 70 to 77) (g)[a]							
	2 5 ± 1 6 § N=30	2 9 ± 2 0 N=29	0 1 ± 2 0 N=30	-0 4 ± 2 4 N=30	3 0 ± 1 8 N=30	-1 1 ± 2 4 N=30	-3 9 ± 2 5 N=30
Body Weight Change (sd 77 to 84) (g)[a]							
	11 4 ± 1 3 N=30	12 3 ± 1 0 N=29	13 7 ± 1 3 N=30	12 2 ± 1 9 N=30	10 1 ± 1 6 N=30	13 2 ± 1 5 N=30	11 3 ± 1 5 N=30

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of dosing
[b]Decrease in N is due to male 173 being euthanized moribund on study day 57
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test.
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶p<0 05, Kruskal-Wallis Test
¶¶p<0 01, Kruskal-Wallis Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥p<0 05, Jonckheere's Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

[redacted]

Table 6 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75 000	750.000	7500 000
No Females on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]	172 3 ± 2 2 N=30	173 9 ± 1 6 N=30	172 3 ± 1.6 N=30	174 5 ± 1 5 N=30	171 8 ± 2 0 N=30	171 5 ± 1 9 N=30	172.1 ± 1 6 N=30
Body Weight (sd 7) (g)[a]	200 5 ‡‡‡ ± 2 1 §§§ N=30	200 8 ± 2 1 N=30	200 4 ± 2 2 N=30	199 5 ± 2 4 N=30	198 7 ± 1 8 N=30	192 2 * ± 2.0 N=30	168 3 *** ± 2.2 N=30
Body Weight (sd 14) (g)[a]	218 4 ‡‡‡ ± 3.0 §§§ N=30	218.3 ± 3 4 N=30	220 1 ± 2 4 N=30	219 3 ± 3 1 N=30	218 2 ± 2 5 N=30	208 2 * ± 2 1 N=30	183.4 *** ± 2 4 N=30
Body Weight (sd 21) (g)[a]	229 7 ‡‡‡ ± 3 2 §§§ N=30	229.4 ± 3 0 N=30	230 6 ± 3.0 N=30	230 7 ± 3 2 N=30	229 6 ± 2.4 N=30	217 8 * ± 2 0 N=30	195.7 *** ± 2 4 N=30
Body Weight (sd 28) (g)[a]	243.2 ‡‡‡ ± 3 9 §§§ N=30	242.9 ± 3.6 N=30	245 6 ± 3 0 N=30	245 3 ± 3 7 N=30	243 4 ± 2 7 N=30	231 3 * ± 2 5 N=30	209.9 *** ± 2 8 N=30
Body Weight (sd 35) (g)[a]	253 0 ‡‡‡ ± 4 4 §§§ N=30	251 6 ± 3 8 N=30	257 1 ± 3 8 N=30	254 7 ± 4 1 N=30	252 5 ± 2 9 N=30	237 1 ** ± 2 6 N=30	217.9 *** ± 2 6 N=30

(continued)

Table 6 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight (sd 42) (g)[a]							
	265 8 ‡‡‡ ± 4 8 §§§ N=30	263 3 ± 4 3 N=30	268 3 ± 3.8 N=30	265 9 ± 4 4 N=30	263 8 ± 3 2 N=30	246 2 ** ± 2 8 N=30	225 0 *** ± 3 0 N=30
Body Weight (sd 49) (g)[a]							
	269 2 ‡‡‡ ± 4.7 §§§ N=30	267.9 ± 4 0 N=30	273 9 ± 4.3 N=30	270 6 ± 4 7 N=30	271 8 ± 3 4 N=30	250 9 ** ± 2 9 N=30	227 2 *** ± 3 0 N=30
Body Weight (sd 56) (g)[a]							
	282 7 ‡‡‡ ± 4 9 §§§ N=30	286 4 ± 4 6 N=30	290 0 ± 4 1 N=30	288 0 ± 5.5 N=30	285 1 ± 3 9 N=30	261 5 ** ± 3 4 N=30	234 8 *** ± 2 7 N=30
Body Weight (sd 63) (g)[a]							
	292 9 ‡‡‡ ± 4 9 §§§ N=30	302 9 ± 5 9 N=30	299 3 ± 4 4 N=30	297 8 ± 6 2 N=30	295 5 ± 4 3 N=30	270 2 ** ± 4 2 N=30	243.0 *** ± 3 3 N=30
Body Weight (sd 70) (g)[a]							
	293 7 ‡‡‡ ± 5 1 §§§ N=30	298.3 ± 5 3 N=30	295 7 ± 4.4 N=30	294 5 ± 5.6 N=30	292 9 ± 3 8 N=30	272 2 ** ± 3 7 N=30	240.8 *** ± 2.6 N=30
Body Weight (sd 77) (g)[a,b]							
	± N=0	± N=0	± N=0	334 8 ± N=1	± N=0	± N=0	255.4 ± 4 9 N=2

(continued)

Table 6 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight Change (sd 0 to 7) (g)[a]							
	28 2 ‡‡‡ ± 1 5 §§§ N=30	26 9 ± 1 1 N=30	28 1 ± 1 4 N=30	25 0 ± 1 7 N=30	26 9 ± 1 4 N=30	20 7 ** ± 1 1 N=30	-3 9 *** ± 1 8 N=30
Body Weight Change (sd 7 to 14) (g)[a]							
	17 9 ± 1 6 § N=30	17 5 ± 2 1 N=30	19 7 ± 1 1 N=30	19 8 ± 1 4 N=30	19 4 ± 1 4 N=30	16 0 ± 1 5 N=30	15 1 ± 1 8 N=30
Body Weight Change (sd 14 to 21) (g)[a]							
	11 3 ± 1 3 N=30	11 2 ± 1 6 N=30	10 5 ± 1 0 N=30	11 4 ± 1 3 N=30	11 5 ± 1 2 N=30	9 5 ± 1 0 N=30	12 3 ± 1 8 N=30
Body Weight Change (sd 21 to 28) (g)[a]							
#	13 6 ± 1 4 N=30	13'5 ± 1 7 N=30	15.0 ± 0 9 N=30	14.6 ± 1 3 N=30	13 8 ± 0 9 N=30	13 6 ± 1 8 N=30	14.2 ± 0.9 N=30
Body Weight Change (sd 28 to 35) (g)[a]							
	9 8 ± 1 5 N=30	8 7 ± 1 2 N=30	11 4 ± 1 3 N=30	9 3 ± 1.2 N=30	9 1 ± 1 4 N=30	5 8 ± 1 7 N=30	8 0 ± 0 8 N=30
Body Weight Change (sd 35 to 42) (g)[a]							
	12 8 ± 1 5 §§ N=30	11.6 ± 1 2 N=30	11.2 ± 1 7 N=30	11 2 ± 1 1 N=30	11 3 ± 1 3 N=30	9 1 ± 1.2 N=30	7 2 ± 1.1 N=30

(continued)

[redacted]

Table 6 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 4 of 5)

		Bisphenol A (ppm in the feed)						
		0 000	0.015	0 300	4 500	75 000	750 000	7500.000
Body Weight Change (sd 42 to 49) (g)[a]		3 4 ± 1 2 § N=30	4 7 ± 1 3 N=30	5 6 ± 1 6 N=30	4 7 ± 1 0 N=30	8 0 ± 1 3 N=30	4 7 ± 1.5 N=30	2.2 ± 0 8 N=30
Body Weight Change (sd 49 to 56) (g)[a]	#	13 5 ¶¶¶ ± 1 9 ¥¥¥ N=30	18 4 ± 2 0 N=30	16 2 ± 2 0 N=30	17 4 ± 1 9 N=30	13.3 ± 2 2 N=30	10 6 ± 1 5 N=30	7.6 ¤¤ ± 0 9 N=30
Body Weight Change (sd 56 to 63) (g)[a]		10 2 ‡ ± 2 2 N=30	16 6 ± 2 2 N=30	9 3 ± 1 9 N=30	9.8 ± 1 8 N=30	10 4 ± 1 9 N=30	8 8 ± 1 7 N=30	8 2 ± 1 3 N=30
Body Weight Change (sd 63 to 70) (g)[a]		0 8 ± 2 6 N=30	-4 6 ± 1 9 N=30	-3.7 ± 2 0 N=30	-3 3 ± 1 8 N=30	-2 5 ± 2 1 N=30	2.0 ± 2.4 N=30	-2.2 ± 1 1 N=30
Body Weight Change (sd 0 to 70) (g)[a]	#	121.4 ¶¶¶ ± 4 9 ¥¥¥ N=30	124 4 ± 4 6 N=30	123 4 ± 3.9 N=30	120.0 ± 5 0 N=30	121 1 ± 4 1 N=30	100 7 ¤¤¤ ± 3 0 N=30	68 7 ¤¤¤ ± 2 3 N=30
Body Weight Change (sd 70 to 77) (g)[a,b]		± N=0	± N=0	± N=0	-15 0 ± N=1	± N=0	± N=0	16.6 ± 2 5 N=2

(continued)

Table 6 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 5 of 5)

---

[a]Reported as the mean ± S E M ; sd=study day with study day 0 being the first day of dosing
[b]Includes all females that had not yet been found sperm and/or plug positive Statistical analyses were not performed on these endpoints since not all females were represented
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend.
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤¤p<0 01; Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 10 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During Gestation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75.000	750.000	7500 000
No Sperm Positive Pregnant Females	26	26	27	27	27	27	28
Body Weight (gd 0) (g)[a]	291 3 ‡‡‡ ± 5 4 §§§ N=26	297 7 ± 5 9 N=26	292.5 ± 4 5 N=27	295 4 ± 6 3 N=27	289 6 ± 4 2 N=27	267 6 ** ± 4 4 N=27	243.4 *** ± 2 9 N=28
Body Weight (gd 7) (g)[a]	317 6 ‡‡‡ ± 5 2 §§§ N=26	323.1 ± 5 5 N=26	317 7 ± 4 3 N=27	320 4 ± 6 4 N=27	315.7 ± 4 2 N=27	290.9 *** ± 4 0 N=27	260.7 *** ± 3 4 N=28
Body Weight (gd 14) (g)[a]	346 7 ‡‡‡ ± 5 3 §§§ N=26	349 3 ± 5 6 N=26	345 2 ± 4.7 N=27	346 7 ± 6 4 N=27	341 6 ± 4 2 N=27	318 2 *** ± 4 7 N=27	277 7 *** ± 3.8 N=28
Body Weight (gd 20) (g)[a]	416 6 ‡‡‡ ± 6 3 §§§ N=26	421 9 ± 7 5 N=26	419 4 ± 5.7 N=26[b]	414 1 ± 7.6 N=27	407 8 ± 6 1 N=27	386 1 ** ± 5.7 N=27	333.1 *** ± 5 7 N=28
Body Weight Change (gd 0 to 7) (g)[a]	26 2 ‡‡ ± 1 4 §§§ N=26	25 3 ± 1 5 N=26	25.3 ± 1 9 N=27	25 0 ± 1 3 N=27	26 2 ± 1 8 N=27	23 2 ± 1 6 N=27	17 3 ** ± 2 0 N=28
Body Weight Change (gd 7 to 14) (g)[a] #	29 1 ¶¶¶ ± 1 3 ¥¥¥ N=26	26 3 ± 1 1 N=26	27 4 ± 1.9 N=27	26 4 ± 1 1 N=27	25 9 ± 1 3 N=27	27 3 ± 1 8 N=27	17 0 ¤¤¤ ± 2 1 N=28

(continued)

Table 10 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During Gestation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500.000
Body Weight Change (gd 14 to 20) (g)[a]							
	69 9 ‡‡‡ ± 2 5 §§§ N=26	72 6 ± 3 1 N=26	73 5 ± 2 4 N=26[b]	67 4 ± 2 4 N=27	66 2 ± 3 6 N=27	67 9 ± 3 1 N=27	55.4 ** ± 2.6 N=28
Body Weight Change (gd 0 to 20) (g)[a]							
	125 2 ‡‡‡ ± 3 3 §§§ N=26	124 2 ± 3 2 N=26	126 7 ± 3 4 N=26[b]	118 8 ± 3 5 N=27	118 2 ± 4 2 N=27	118 5 ± 3 1 N=27	89 8 *** ± 4 9 N=28

[a]Reported as the mean ± S E M , gd=gestational day
[b]Decrease in N is due to female 316 being in the process of delivering at the time of weighing on gestational day 20 and was therefore the body weight was not taken
#Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§§§p<0 001, Test for Linear Trend
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 13 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During Lactation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
No Females with Litters on Postnatal Day 0	26	26	27	27	26[a]	27	27[a]
Body Weight (pnd 0) (g)[b]							
	323 2 ‡‡‡ ± 5 5 §§§ N=26	327 4 ± 5 4 N=26	323 3 ± 3 9 N=27	323 2 ± 5 7 N=27	315.1 ± 4 4 N=26	299 5 ** ± 4 6 N=27	255 2 *** ± 4 2 N=27
Body Weight (pnd 4) (g)[b]							
	340 5 ‡‡‡ ± 5 4 §§§ N=25[c]	339 3 ± 5.8 N=26	333.5 ± 3 6 N=27	334 6 ± 6 4 N=27	329 6 ± 5 1 N=26	313 6 ** ± 4 1 N=27	258 8 *** ± 3 7 N=27
Body Weight (pnd 7) (g)[b]							
	344 2 ‡‡‡ ± 5 5 §§§ N=25	345 1 ± 5 4 N=26	337 5 ± 3 8 N=27	338 8 ± 5 8 N=26[d]	338.3 ± 4.5 N=26	322 6 ** ± 3 9 N=27	272 7 *** ± 4 6 N=27
Body Weight (pnd 14) (g)[b]							
	351 1 ‡‡‡ ± 5 1 §§§ N=25	353 8 ± 5 1 N=26	346 9 ± 3 6 N=27	350 2 ± 6.0 N=27	340 2 ± 4 2 N=26	326 9 ** ± 4 4 N=27	288 3 *** ± 5 2 N=27
Body Weight (pnd 21) (g)[b]							
	341 3 ‡‡‡ ± 5 0 §§§ N=25	344 2 ± 4 9 N=26	334.8 ± 4 3 N=27	333 7 ± 5 6 N=27	335 1 ± 3 2 N=26	327 0 ± 4 6 N=27	291 1 *** ± 4 6 N=27

(continued)

Table 13 Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Changes During Lactation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (pnd 0 to 4) (g)[b]							
	16 2 ‡ ± 2 2 §§§ N=25	11 9 ± 3 1 N=26	10 2 ± 2 2 N=27	11 5 ± 2 5 N=27	14 5 ± 2 9 N=26	14 1 ± 2 8 N=27	3.6 ** ± 1.9 N=27
Body Weight Change (pnd 4 to 7) (g)[b]							
	3 7 ± 2 8 §§ N=25	5 8 ± 2 2 N=26	4 0 ± 3 0 N=27	6 3 ± 3 5 N=26[c]	8 8 ± 3 0 N=26	9 1 ± 2 5 N=27	13 9 ± 2 0 N=27
Body Weight Change (pnd 7 to 14) (g)[b]							
	6 9 ± 3 6 § N=25	8 8 ± 2 7 N=26	9 3 ± 3 5 N=27	9 7 ± 3 3 N=26[d]	1 9 ± 3 8 N=26	4 3 ± 4 4 N=27	15 6 ± 3 7 N=27
Body Weight Change (pnd 14 to 21) (g)[b]							
	-9 8 ‡‡‡ ± 3 3 §§§ N=25	-9 7 ± 2 1 N=26	-12 1 ± 2 9 N=27	-16 5 ± 2 8 N=27	-5 0 ± 3 0 N=26	0 0 ± 2 6 N=27	2 8 * ± 3 5 N=27
Body Weight Change (pnd 0 to 21) (g)[b]							
	17.0 ‡‡‡ ± 4 4 §§§ N=25	16 8 ± 3 9 N=26	11 5 ± 3 7 N=27	10 5 ± 3 1 N=27	20 1 ± 2 5 N=26	27 5 ± 4.3 N=27	35 9 ** ± 3 6 N=27

[a]One female was pregnant but did not deliver a litter (had implant sites only)
[b]Reported as the mean ± S E M , pnd=postnatal day
[c]Decrease in N is due to the entire litter of female 328 being dead or euthanized moribund on or before postnatal day 3
[d]Decrease in N is due to the postnatal day 7 body weight for one female inadvertently not being recorded

‡p<0 05, ANOVA Test ‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend. §§p<0 01, Test for Linear Trend §§§p<0 001; Test for Linear Trend
*p<0 05, Dunnett's Test **p<0 01, Dunnett's Test ***p<0 001, Dunnett's Test

Table 16 Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75 000	750.000	7500 000
No Animals Started on Study							
Males	30	30	30	30	30	30	30
Females	30	30	30	30	30	30	30
No Females Paired							
	30	30	30	30	30	30	30
No of Females that Mated							
	30	30	30	30	30	30	30
Mating Index (no females that mated/no females paired)							
	100 0	100 0	100 0	100 0	100 0	100 0	100 0
No of Pregnant Females							
	26	26	27	27	27	27	28
Fertility Index (no pregnant females/no females that mated)							
	86 7	86 7	90 0	90 0	90 0	90 0	93 3
No of Females with Live Litters (pnd 0)							
	26	26	27	27	26[a]	27	27[b]
Gestational Index (no females with live litters/no females pregnant)							
	100 0	100 0	100.0	100 0	96 3	100 0	96 4

(continued)

Table 16 Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4.500	75 000	750 000	7500 000
No Males Paired	30	29[c]	30	30	30	30	30
No Males that Mated	30	29	30	30	30	30	30
Mating Index (no males that mated/no males paired)	100 0	100 0	100 0	100 0	100 0	100 0	100.0
No Males Siring Litters	26	25	27	27	27	27	28
Fertility Index (no males siring litters/no males that mated)	86 7	86 2	90 0	90 0	90 0	90 0	93 3
Pregnancy Index (no pregnant females/no males that mated)	86 7	89 7	90 0	90 0	900 0	90 0	93 3
Days Until Sperm Positive (days)[d,e] #	2 3 ± 0 2 N=30	2.4 ± 0 2 N=30	2 3 ± 0.2 N=30	2 9 ± 0 3 N=30	2 4 ± 0 2 N=30	2 3 ± 0 2 N=30	3 4 ± 0 5 N=30
Gestational Length (days)[d,f]	22 1 ± 0 1 N=26	22 1 ± 0 1 N=26	22 1 ± 0 1 N=27	22 1 ± 0 1 N=27	22.2 ± 0 1 N=26	22 0 ± 0 1 N=27	22 1 ± 0 1 N=27

(continued)

Table 16 Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75.000	750.000	7500 000
No of Live Litters							
Postnatal Day 0	26	26	27	27	26	27	27
Postnatal Day 4	25	26	27	27	26	27	27
Postnatal Day 7	25	26	27	27	26	27	27
Postnatal Day 14	25	26	27	27	26	27	27
Postnatal Day 21	25	26	27	27	26	27	27
No Implantation Sites per Litter[d]							
	14 23 ‡‡ ± 0 62 §§§ N=26	15.04 ± 0 51 N=26	14 93 ± 0 49 N=27	13 93 ± 0 61 N=27	14 74 ± 0 64 N=27	14.04 ± 0 48 N=27	11 89 ** ± 0 52 N=28
Percent Postimplantation Loss per Litter[d]							
#	3 45 ± 1 23 ¥¥ N=26	6 96 ± 2 67 N=26	7.02 ± 1 70 N=27	5 66 ± 1 48 N=27	13 81 ± 4 21 N=27	9 96 ± 3 03 N=27	11.33 ± 3.64 N=28
Number of Live Pups on Postnatal Day 0[d]							
	14 3 ‡‡ ± 0 6 §§§ N=26	14 7 ± 0.7 N=26	14.1 ± 0 5 N=27	13 3 ± 0 6 N=27	13 7 ± 0.5 N=26	12 9 ± 0 6 N=27	11 5 ** ± 0 4 N=27
Number of Dead Pups on Postnatal Day 0[d]							
#	0 0 ± 0 0 N=26	0 2 ± 0 1 N=26	0 1 ± 0 1 N=27	0 2 ± 0 2 N=27	0 3 ± 0 1 N=26	0 2 ± 0 1 N=27	0 3 ± 0 1 N=27
Total Number of Pups on Postnatal Day 0[d]							
	14 4 ‡‡ ± 0.6 §§§ N=26	14 9 ± 0.7 N=26	14.3 ± 0 5 N=27	13.5 ± 0.6 N=27	14 0 ± 0.5 N=26	13 1 ± 0 6 N=27	11 8 ** ± 0 4 N=27

(continued)

Table 16 Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750.000	7500 000
Stillbirth Index (no dead on pnd 0/total no on pnd 0)[d]							
#	0 2 ± 0 2 N=26	1 8 ± 0 8 N=26	0 8 ± 0 6 N=27	1 8 ± 0.8 N=27	2 1 ± 1 0 N=26	1 5 ± 0.7 N=27	2.1 ± 0 8 N=27
Live Birth Index (no live on pnd 0/total no. on pnd 0)[d]							
#	99 8 ± 0 2 N=26	98.2 ± 0 8 N=26	99 2 ± 0 6 N=27	98 2 ± 0 8 N=27	97 9 ± 1 0 N=26	98 5 ± 0 7 N=27	97 9 ± 0 8 N=27
4 Day Survival Index (no surviving 4 days/no live on pnd 0)[d]							
#	95 2 ± 3 8 N=26	98 1 ± 0.6 N=26	99 4 ± 0 4 N=27	98 9 ± 0 7 N=27	99 8 ± 0 2 N=26	98 2 ± 0 9 N=27	99.0 ± 0.7 N=27
7 Day Survival Index (no surviving 7 days/no live on pnd 4)[d]							
#	100 0 ± 0 0 N=25[g]	100 0 ± 0 0 N=26	100 0 ± 0 0 N=27	100 0 ± 0 0 N=27	100 0 ± 0 0 N=26	100 0 ± 0 0 N=27	98 5 ± 1 2 N=27
14 Day Survival Index (no. surviving 14 days/no live on pnd 7)[d]							
#	99 6 ± 0 4 N=25	100 0 ± 0 0 N=26	100 0 ± 0 0 N=27	100.0 ± 0 0 N=27	100.0 ± 0 0 N=26	99 6 ± 0 4 N=27	100 0 ± 0 0 N=27
21 Day Survival Index (no surviving 21 days/no live on pnd 14)[d]							
#	100 0 ± 0 0 N=25	99 6 ± 0 4 N=26	100 0 ± 0 0 N=27	99 6 ± 0 4 N=27	100 0 ± 0.0 N=26	100.0 ± 0 0 N=27	99 3 ± 0 7 N=27

(continued)

[redacted]

Table 16 Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Lactational Index (no surviving 21 days/no live on pnd 4)[d]							
#	99 6 ± 0 4 N=25	99 6 ± 0 4 N=26	100 0 ± 0 0 N=27	99 6 ± 0 4 N=27	100 0 ± 0 0 N=26	99 6 ± 0 4 N=27	97 8 ± 1 3 N=27

[a]Female 308 had implant sites only
[b]Female 372 had implant sites only.
[c]Male 173 was euthanized moribund on study day 57 prior to mating
[d]Reported as the mean ± S E M , pnd=postnatal day. All indexes are the average percent per litter
[e]Days until sperm positive could only be calculated for those females for which sperm were detected in the vaginal smear
[f]Gestational length could not be calculated for females that were pregnant, but for which sperm were never detected in the vaginal smear
[g]The entire litter for female 328 was dead or missing and presumed dead on or before postnatal day 3
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
¥¥P<0 01, Jonckheere's Test
‡‡p<0 01, ANOVA Test
§§§p<0 001, Test for Linear Trend
**p<0 01; Dunnett's Test

[redacted]

Table 17 Summary and Statıstıcal Analysıs of the F_1 Litter Sıze, F_1 Pup Body Weıghts, Percent F_1 Males and F_1 Male Nipple Evaluations Durıng Lactatıon (page 1 of 6)

	Bısphenol A (ppm ın the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
No of Lıve Lıtters							
Postnatal Day 0	26	26	27	27	26	27	27
Postnatal Day 4	25[a]	26	27	27	26	27	27
Postnatal Day 7	25	26	27	27	26	27	27
Postnatal Day 14	25	26	27	27	26	27	27
Postnatal Day 21	25	26	27	27	26	27	27
Average Number of Lıve Pups per Lıtter (pnd 0)[b]							
	14 3 ‡‡ ± 0 6 §§§ N=26	14 7 ± 0 7 N=26	14 1 ± 0 5 N=27	13 3 ± 0 6 N=27	13 7 ± 0 5 N=26	12.9 ± 0 6 N=27	11.5 ** ± 0.4 N=27
Average Number of Lıve Pups per Lıtter (pnd 4)[b]							
	13 7 ‡‡ ± 0 8 §§§ N=26	14 4 ± 0.7 N=26	14 1 ± 0 5 N=27	13 2 ± 0 6 N=27	13 7 ± 0 5 N=26	12.6 ± 0 6 N=27	11 4 ** ± 0.4 N=27
Average Number of Lıve Pups per Lıtter (pnd 7)[b]							
#	9 7 ± 0 2 N=25	9 6 ± 0 3 N=26	9 8 ± 0 2 N=27	9 5 ± 0 2 N=27	9 8 ± 0 2 N=26	9 4 ± 0 3 N=27	9 6 ± 0.2 N=27
Average Number of Lıve Pups per Lıtter (pnd 14)[b]							
#	9 6 ± 0 2 N=25	9 6 ± 0 3 N=26	9 8 ± 0 2 N=27	9 5 ± 0 2 N=27	9 8 ± 0 2 N=26	9 4 ± 0 3 N=27	9.6 ± 0.2 N=27
Average Number of Live Pups per Litter (pnd 21)[b]							
#	9 6 ± 0 2 N=25	9 5 ± 0 3 N=26	9 8 ± 0 2 N=27	9 5 ± 0 2 N=27	9 8 ± 0.2 N=26	9 4 ± 0 3 N=27	9 6 ± 0 2 N=27

(contınued)

Table 17 Summary and Statistical Analysis of the F_1 Litter Size, F_1 Pup Body Weights, Percent F_1 Males and F_1 Male Nipple Evaluations During Lactation (page 2 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Average Pup Body Weight (g) per Litter (pnd 0)[b]							
	6 37 ± 0 12 N=26	6 25 ± 0 13 N=26	6 47 ± 0 11 N=27	6 37 ± 0 10 N=27	6 45 ± 0 12 N=26	6 33 ± 0 17 N=27	6.17 ± 0 10 N=27
Average **Male** Body Weight (g) per Litter (pnd 0)[b]							
	6 53 ± 0 11 N=26	6 36 ± 0 14 N=26	6 69 ± 0 12 N=27	6 60 ± 0 10 N=27	6 62 ± 0 12 N=26	6 49 ± 0 17 N=27	6 37 ± 0 11 N=26[c]
Average **Female** Body Weight (g) per Litter (pnd 0)[b]							
	6.19 ± 0 12 N=26	6 10 ± 0 12 N=26	6.29 ± 0 12 N=27	6 17 ± 0 10 N=27	6 27 ± 0 12 N=26	6.18 ± 0 18 N=27	6.00 ± 0 09 N=27
Average Pup Body Weight (g) per Litter (pnd 4)[b]							
	10 46 ‡‡ ± 0.25 §§§ N=25	10 23 ± 0 30 N=26	10 58 ± 0 28 N=27	10 88 ± 0 30 N=27	10 74 ± 0 27 N=26	10 45 ± 0 41 N=27	9.32 * ± 0.23 N=27
Average **Male** Body Weight (g) per Litter (pnd 4)[b]							
	10 72 ‡ ± 0.25 §§§ N=25	10 35 ± 0 31 N=26	10 88 ± 0 30 N=27	11 20 ± 0 30 N=27	10 95 ± 0 27 N=26	10 65 ± 0.40 N=27	9 63 ± 0 26 N=26[c]
Average **Female** Body Weight (g) per Litter (pnd 4)[b]							
	10 17 ‡ ± 0 24 §§§ N=25	10 09 ± 0 30 N=26	10 31 ± 0 28 N=27	10 60 ± 0 30 N=27	10 54 ± 0 29 N=26	10 27 ± 0 43 N=27	9 08 ± 0 22 N=27

(continued)

Table 17 Summary and Statistical Analysis of the F_1 Litter Size, F_1 Pup Body Weights, Percent F_1 Males and F_1 Male Nipple Evaluations During Lactation (page 3 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Average Pup Body Weight (g) per Litter (pnd 7)[b]							
	16.93 ‡‡‡	16.27	16 57	17 17	16 84	16 23	13.09 ***
	± 0 32 §§§	± 0 37	± 0 33	± 0 44	± 0 37	± 0 57	± 0.34
	N=25	N=26	N=27	N=26[d]	N=26	N=27	N=27
Average **Male** Body Weight (g) per Litter (pnd 7)[b]							
	17 39 ‡‡‡	16.42	17 09	17 68	17.17	16 51	13.54 ***
	± 0 35 §§§	± 0 39	± 0 36	± 0 46	± 0 38	± 0 56	± 0 37
	N=25	N=26	N=27	N=26[d]	N=26	N=27	N=26[c]
Average **Female** Body Weight (g) per Litter (pnd 7)[b]							
	16 45 ‡‡‡	16.20	16 10	16 67	16 57	16.00	12 75 ***
	± 0 29 §§§	± 0 38	± 0 33	± 0 42	± 0 41	± 0 61	± 0 35
	N=25	N=26	N=27	N=26[d]	N=26	N=27	N=27
Average Pup Body Weight (g) per Litter (pnd 14)[b]							
	33 46 ‡‡‡	32 36	32 69	33 63	32 84	31 71	24 43 ***
	± 0 52 §§§	± 0 70	± 0 47	± 0 69	± 0 50	± 0 83	± 0 56
	N=25	N=26	N=27	N=27	N=26	N=27	N=27
Average **Male** Body Weight (g) per Litter (pnd 14)[b]							
	34 15 ‡‡‡	32 75	33 48	34 44	33 46	32 28	25 17 ***
	± 0 58 §§§	± 0 72	± 0 53	± 0 72	± 0 54	± 0 81	± 0 65
	N=25	N=26	N=27	N=27	N=26	N=27	N=26[c]
Average **Female** Body Weight (g) per Litter (pnd 14)[b]							
	32.70 ‡‡‡	32.03	31.95	32 86	32 23	31 17	23 92 ***
	± 0 48 §§§	± 0 73	± 0 47	± 0 67	± 0 51	± 0 87	± 0.51
	N=25	N=26	N=27	N=27	N=26	N=27	N=27

(continued)

[redacted]

Table 17 Summary and Statistical Analysis of the F_1 Litter Size, F_1 Pup Body Weights, Percent F_1 Males and F_1 Male Nipple Evaluations During Lactation (page 4 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Average Pup Body Weight (g) per Litter (pnd 21)[b]							
#	49.34 ¶¶¶	47 35 ¤	47 81	48 85	47 18 ¤	47 33 ¤	36 10 ¤¤¤
	± 0 74 ¥¥¥	± 1 15	± 0 91	± 1 24	± 0 73	± 1 39	± 0 73
	N=25	N=26	N=27	N=27	N=26	N=27	N=27
Average **Male** Body Weight (g) per Litter (pnd 21)[b]							
	50 77 ‡‡‡	48 11	49 41	50 54	48 42	48 33	37.21 ***
	± 0 90 §§§	± 1 20	± 0 97	± 1.36	± 0.90	± 1.34	± 0.93
	N=25	N=26	N=27	N=27	N=26	N=27	N=26[c]
Average **Female** Body Weight (g) per Litter (pnd 21)[b]							
#	47 82 ¶¶¶	46.65	46 25 ¤	47 28	45.96	46 37 ¤	35.22 ¤¤¤
	± 0 59 ¥¥¥	± 1.14	± 0 94	± 1 11	± 0 68	± 1 48	± 0.62
	N=25	N=26	N=27	N=27	N=26	N=27	N=27
Percent Male Pups per Litter (pnd 0)[b]							
	49 2	53 0	47 2	46 1	54 1	52 8	45 3
	± 3 0	± 2 5	± 2.6	± 2 3	± 3 1	± 2 0	± 3 0
	N=26	N=26	N=27	N=27	N=26	N=27	N=27
Percent Male Pups per Litter (pnd 4)[b]							
	49 8	52 6	47 9	46 8	53 9	52 5	45 7
	± 3 3	± 2 8	± 2.7	± 2 3	± 3 1	± 2 1	± 3.0
	N=25	N=26	N=27	N=27	N=26	N=27	N=27
Percent Male Pups per Litter (pnd 7)[b]							
#	50 7	51 9	48 2	48 0	51 3	51 4	46 5
	± 2 2	± 1 8	± 1 7	± 1 8	± 2 3	± 1 3	± 2 7
	N=25	N=26	N=27	N=27	N=26	N=27	N=27

(continued)

Table 17 Summary and Statistical Analysis of the F_1 Litter Size, F_1 Pup Body Weights, Percent F_1 Males and F_1 Male Nipple Evaluations During Lactation (page 5 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0.300	4 500	75.000	750 000	7500 000
Percent Male Pups per Litter (pnd 14)[b]							
#	51 0 ± 2 2 N=25	51 9 ± 1 8 N=26	48 6 ± 1.6 N=27	48.0 ± 1 8 N=27	51 3 ± 2 3 N=26	51 1 ± 1 3 N=27	46 5 ± 2 7 N=27
Percent Male Pups per Litter (pnd 21)[b]							
#	51 0 ± 2 2 N=25	51.7 ± 1 9 N=26	48 6 ± 1 6 N=27	48 2 ± 1 8 N=27	51 3 ± 2 3 N=26	51 1 ± 1 3 N=27	46 7 ± 2 6 N=27
No of Nipples per Animal[e]							
	0 00 ± 0 00 N=123	0 00 ± 0.00 N=130	0 00 ± 0 00 N=130	0 00 ± 0 00 N=123	0 00 ± 0 00 N=132	0.00 ± 0 00 N=130	0.00 ± 0.00 N=121
Percent with One or More Nipples							
	0 00	0 00	0 00	0 00	0 00	0 00	0 00
No of Areolae per Animal[e]							
	0 00 ± 0.00 N=123	0 02 ± 0 02 N=130	0 00 ± 0 00 N=130	0 01 ± 0 01 N=123	0 06 ± 0 04 N=132	0 04 ± 0.03 N=130	0 01 ± 0 01 N=121
Percent with One or More Areolae							
	0 00	0 77	0 00	0 81	3 03	2.31	0.83

(continued)

Table 17 Summary and Statistical Analysis of the F_1 Litter Size, F_1 Pup Body Weights, Percent F_1 Males and F_1 Male Nipple Evaluations During Lactation (page 6 of 6)

[a]The entire litter for female 328 was dead or missing and presumed dead on or before postnatal day 3.
[b]Reported as the mean ± S.E M , pnd=postnatal day
[c]Decrease in N is due to one female having a litter of all female pups
[d]Decrease in N is due to the body weights on postnatal day 7 inadvertently not being recorded for one litter.
[e]Reported as the mean ± S E M (adjusted for intralitter correlations)
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 22 Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Post-Mating Holding Period (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0.300	4.500	75.000	750.000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 84) (g)[a]							
	516 3 ‡‡‡ ± 8 3 §§§ N=30	504 6 ± 6 5 N=29[b]	505 9 ± 7 8 N=30	517 6 ± 7 9 N=30	522 0 ± 9 0 N=30	492 6 ± 9.9 N=30	408 4 *** ± 5 9 N=30
Body Weight (sd 91) (g)[a]							
	530 2 ‡‡‡ ± 8 3 §§§ N=30	516 5 ± 6 8 N=29	520 5 ± 8 0 N=30	532 6 ± 8 0 N=30	534.2 ± 9 6 N=30	507 9 ± 10 3 N=30	417 2 *** ± 6 4 N=30
Body Weight (sd 98) (g)[a]							
	536 5 ‡‡‡ ± 8 3 §§§ N=30	523 9 ± 6 7 N=29	528 0 ± 8.4 N=30	537 9 ± 8 1 N=30	541.9 ± 9 6 N=30	514 5 ± 10 4 N=30	425 2 *** ± 6 2 N=30
Body Weight (sd 105) (g)[a]							
	541 8 ‡‡‡ ± 8.8 §§§ N=30	529 3 ± 7.1 N=29	531 7 ± 8.5 N=30	542 1 ± 8 5 N=30	544 6 ± 10.0 N=30	517.3 ± 10.5 N=30	425 8 *** ± 6 6 N=30
Body Weight Change (sd 84 to 91) (g)[a]							
#	13.9 ¶ ± 0 8 N=30	11.9 ± 1 1 N=29	14 6 ± 0 8 N=30	15 0 ± 1 0 N=30	12.2 ± 2 0 N=30	15 3 ± 1 2 N=30	8 8 ¤ ± 2 3 N=30

(continued)

Table 22 Summary and Statistical Analysis of the F_0 Male Body Weights and Weight Changes During the Post-Mating Holding Period (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750 000	7500.000
Body Weight Change (sd 91 to 98) (g)[a]							
	6 3 ± 1 1 N=30	7.5 ± 1 1 N=29	7 6 ± 1 2 N=30	5 3 ± 1 3 N=30	7 7 ± 1 2 N=30	6.6 ± 0.7 N=30	7 9 ± 1 5 N=30
Body Weight Change (sd 98 to 105) (g)[a]							
	5 3 ± 1 2 §§ N=30	5 4 ± 1.0 N=29	3 6 ± 1 0 N=30	4 2 ± 1 5 N=30	2 7 ± 1 2 N=30	2 8 ± 1 2 N=30	0 6 ± 1 4 N=30

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of dosing
[b]Decrease in N is due to male 173 being euthanized moribund on study day 57
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡‡‡p<0 001, ANOVA Test
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
***p<0 001, Dunnett's Test
¶p<0 05, Kruskal-Wallis Test
¤p<0 05, Mann-Whitney U Test

Table 20 Summary and Statistical Analysis of F_1 Pup Necropsy Weights on Postnatal Day 21 (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
MALES	69	72	76	75	72	78	70
Body Weight at Sacrifice (g)[a]							
	50 16 ΓΓΓ ± 0 88 ßßß N=69	46 65 ◊ ± 0 73 N=72	48 33 ± 0 82 N=76	50 01 ± 1 34 N=75	47 40 ◊ ± 0 77 N=72	47 21 ± 1 06 N=78	37 13 ◊◊◊ ± 1 06 N=70
Liver Weight (g)[a]							
	2 3154 ΓΓΓ ±0 0621 ßßß N=69	2 1229 ±0 0508 N=72	2.2175 ±0 0516 N=76	2 3455 ±0 0885 N=75	2.1325 ±0 0633 N=72	2 1624 ±0 0748 N=78	1 6895 ◊◊◊ ±0 0664 N=70
Thymus Weight (g)[a]							
	0 2318 ΓΓΓ ±0 0071 ßßß N=69	0.2072 ◊ ±0.0056 N=72	0.2300 ±0 0054 N=76	0 2340 ±0.0065 N=75	0 2189 ±0 0066 N=72	0 2166 ±0 0064 N=78	0 1716 ◊◊◊ ±0 0075 N=70
Spleen Weight (g)[a]							
	0 2230 ΓΓΓ ±0 0087 ßßß N=69	0 2029 ±0 0066 N=72	0 2159 ±0 0075 N=76	0 2310 ±0 0100 N=75	0 2053 ±0 0066 N=71[b]	0 1949 ◊ ±0 0062 N=78	0 1406 ◊◊◊ ±0 0066 N=70
Brain Weight (g)[a]							
	1 4726 ΓΓΓ ±0 0129 ßßß N=67[b,c]	1 4384 ±0 0117 N=72	1 4566 ±0 0093 N=76	1 4771 ±0 0140 N=75	1 4690 ±0 0087 N=70[b]	1 4585 ±0 0129 N=76[b,c]	1 3708 ◊◊◊ ±0 0173 N=70
Paired Testes Weight (g)[a]							
	0 2449 ΓΓΓ ±0 0068 ßßß N=69	0.2234 ◊ ±0 0057 N=72	0 2347 ±0 0048 N=76	0.2516 ±0 0067 N=75	0.2363 ±0.0051 N=72	0.2348 ±0 0086 N=77[b]	0 1925 ◊◊◊ ±0 0065 N=70

(continued)

Table 20 Summary and Statistical Analysis of F_1 Pup Necropsy Weights on Postnatal Day 21 (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4.5	75	750	7500
Paired Epididymis Weight (g)[a]							
	0 1051 ΓΓ ±0 0114 ßß N=69	0 0770 ◊ ±0 0060 N=72	0 0799 ±0 0070 N=76	0 0995 ±0 0099 N=75	0 1022 ±0 0090 N=72	0 0892 ±0 0073 N=75[b]	0 0715 ◊◊ ±0 0057 N=70
Seminal Vesicles with Coagulating Gland Weight (g)[a]							
	0 0215 ±0 0011 ß N=69	0 0210 ±0 0011 N=71[d]	0 0206 ±0 0008 N=75[b]	0 0224 ±0 0011 N=74[d]	0 0200 ±0 0012 N=71[b]	0 0203 ±0 0009 N=76[b,d]	0 0184 ±0 0012 N=69[b]
Relative Liver Weight (% of sacrifice weight)[a]							
	4 6067 ±0 0717 N=69	4 5410 ±0 0828 N=72	4 5765 ±0 0564 N=76	4 6636 ±0 0700 N=75	4 4774 ±0 0833 N=72	4 5578 ±0 0805 N=78	4 5216 ±0 0774 N=70
Relative Thymus Weight (% of sacrifice weight)[a]							
	0 4620 ±0.0097 N=69	0 4455 ±0 0123 N=72	0 4765 ±0 0082 N=76	0 4690 ±0 0110 N=75	0 4619 ±0 0110 N=72	0 4596 ±0 0100 N=78	0 4585 ±0 0138 N=70
Relative Spleen Weight (% of sacrifice weight)[a]							
	0 4425 ΓΓΓ ±0 0127 ßßß N=69	0 4321 ±0 0098 N=72	0 4440 ±0 0106 N=76	0 4573 ±0 0102 N=75	0 4319 ±0 0118 N=71[b]	0 4113 ◊ ±0 0068 N=78	0.3770 ◊◊◊ ±0 0099 N=70
Relative Brain Weight (% of sacrifice weight)[a]							
	2 9597 ΓΓΓ ±0 0406 ßßß N=67[b,c]	3 1087 ◊ ±0 0376 N=72	3 0429 ±0 0500 N=76	3 0000 ±0 0591 N=75	3 1220 ◊ ±0 0469 N=70[b]	3 1325 ◊ ±0 0540 N=76[b,c]	3 7634 ◊◊◊ ±0 0896 N=70

(continued)

Table 20 Summary and Statistical Analysis of F_1 Pup Necropsy Weights on Postnatal Day 21 (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0.3	4 5	75	750	7500
Relative Paired Testes Weight (% of sacrifice weight)[a]							
	0 4879 Γ ±0 0080 ßß N=69	0 4779 ±0 0085 N=72	0 4864 ±0 0066 N=76	0 5039 ±0 0073 N=75	0 4990 ±0 0067 N=72	0 4950 ±0 0116 N=77[b]	0 5172 ◊ ±0 0095 N=70
Relative Paired Epididymis Weight (% of sacrifice weight)[a]							
	0 2071 ±0 0206 N=69	0 1659 ±0 0126 N=72	0 1650 ±0 0138 N=76	0 1954 ±0 0164 N=75	0 2130 ±0 0165 N=72	0 1903 ±0 0138 N=75[b]	0 1919 ±0 0135 N=70
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight)[a]							
	0 0430 ±0 0022 N=69	0 0451 ±0 0021 N=71[d]	0 0429 ±0 0015 N=75[b]	0 0448 ±0 0018 N=74[d]	0 0419 ±0 0023 N=71[b]	0 0433 ±0.0018 N=76[b,d]	0 0500 ±0 0030 N=69[b]
FEMALES	70	70	81	77	73	75	77
Body Weight at Sacrifice (g)[a]							
	47 38 ΓΓΓ ± 0 62 ßßß N=70	44 85 ± 0 69 N=70	45 25 ± 1 05 N=81	46 49 ± 0.99 N=77	45 73 ± 0 67 N=73	44 89 ± 1 00 N=75	35 09 ◊◊◊ ± 0 61 N=77
Liver Weight (g)[a]							
	2 2722 ΓΓΓ ±0 0502 ßßß N=70	2 1404 ±0 0439 N=70	2 1870 ±0.0551 N=81	2.2727 ±0 0692 N=77	2.1882 ±0 0530 N=73	2 1560 ±0 0624 N=75	1 6395 ◊◊◊ ±0 0450 N=77
Thymus Weight (g)[a]							
	0 2366 ΓΓΓ ±0 0084 ßßß N=70	0 2205 ±0 0072 N=70	0 2371 ±0 0062 N=80[b]	0 2362 ±0 0065 N=77	0 2317 ±0 0068 N=73	0 2202 ±0 0065 N=75	0 1787 ◊◊◊ ±0 0050 N=77

(continued)

Table 20. Summary and Statistical Analysis of F_1 Pup Necropsy Weights on Postnatal Day 21 (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Spleen Weight (g)[a]							
	0 2110 ΓΓΓ ±0 0065 ßßß N=70	0 1957 ±0 0063 N=70	0 2062 ±0 0077 N=80[b]	0 2138 ±0 0085 N=77	0 2065 ±0 0056 N=73	0 1944 ±0 0084 N=75	0 1339 ◊◊◊ ±0 0048 N=77
Brain Weight (g)[a]							
	1 4095 ΓΓΓ ±0 0117 ßßß N=70	1 4073 ±0 0087 N=70	1 4268 ±0.0106 N=80[b]	1 4128 ±0.0110 N=76[b]	1 4137 ±0 0095 N=72[b]	1 3904 ±0 0116 N=75	1 3058 ◊◊◊ ±0.0135 N=76[b]
Paired Ovary Weight (g)[a]							
	0 0373 ΓΓΓ ±0 0011 ßßß N=70	0 0354 ±0 0011 N=68[b,e]	0.0367 ±0 0010 N=81	0.0375 ±0 0011 N=76[e]	0 0372 ±0 0010 N=73	0 0354 ±0 0013 N=75	0 0267 ◊◊◊ ±0.0009 N=76[b]
Uterus Weight (g)[a]							
	0 1028 ΓΓΓ ±0 0045 ßßß N=70	0 0924 ±0 0035 N=70	0.0901 ◊ ±0 0032 N=81	0 0998 ±0 0053 N=77	0 0923 ±0 0038 N=73	0 0936 ±0 0049 N=74[b]	0 0640 ◊◊◊ ±0 0028 N=77
Relative Liver Weight (% of sacrifice weight)[a]							
	4 7807 ±0 0589 ß N=70	4 7692 ±0 0653 N=70	4 8613 ±0 1055 N=81	4 8633 ±0 0699 N=77	4 7677 ±0 0560 N=73	4 7976 ±0 0777 N=75	4 6545 ±0 0621 N=77
Relative Thymus Weight (% of sacrifice weight)[a]							
	0 4982 ±0 0147 N=70	0 4917 ±0 0141 N=70	0.5263 ±0 0125 N=80[b]	0 5085 ±0 0100 N=77	0 5072 ±0 0128 N=73	0 4927 ±0.0118 N=75	0 5079 ±0 0102 N=77

(continued)

Table 20 Summary and Statistical Analysis of F_1 Pup Necropsy Weights on Postnatal Day 21 (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Spleen Weight (% of sacrifice weight)[a]							
	0 4433 ΓΓΓ ±0 0098 ßßß N=70	0 4335 ±0 0094 N=70	0 4565 ±0 0138 N=80[b]	0 4566 ±0 0125 N=77	0 4502 ±0 0095 N=73	0 4285 ±0 0104 N=75	0 3794 ◊◊◊ ±0 0093 N=77
Relative Brain Weight (% of sacrifice weight)[a]							
	2 9898 ΓΓΓ ±0 0309 ßßß N=70	3 1664 ◊◊ ±0 0499 N=70	3 2133 ◊◊ ±0.0741 N=80[b]	3 0746 ±0 0589 N=76[b]	3 1233 ◊◊ ±0 0395 N=72[b]	3 1401 ◊ ±0 0609 N=75	3 7590 ◊◊◊ ±0.0471 N=76[b]
Relative Paired Ovary Weight (% of sacrifice weight)[a]							
	0 0787 ±0 0041 N=70	0.0788 ±0 0022 N=68[b,e]	0 0819 ±0 0021 N=81	0 0810 ±0 0019 N=76[e]	0 0813 ±0 0020 N=73	0 0787 ±0 0022 N=75	0 0762 ±0 0021 N=76[b]
Relative Uterus Weight (% of sacrifice weight)[a]							
	0 2158 ΓΓ ±0 0081 ßßß N=70	0 2050 ±0 0062 N=70	0 1998 ±0 0062 N=81	0 2113 ±0 0077 N=77	0 2008 ±0 0073 N=73	0 2065 ±0 0080 N=74[b]	0 1809 ◊◊◊ ±0 0063 N=77

[a]Reported as the mean ± S E M (adjusted for intralitter correlations)
[b]Decrease in N is due to one or more weights being statistical outliers and therefore they were removed
[c]Decrease in N is due to one brain weight inadvertently not being recorded
[d]Decrease in N is due to one seminal vesicle weight inadvertently not being recorded.
[e]Decrease in N is due to one ovary weight inadvertently not being recorded
Γp<0 05, Overall analysis of correlated data
ΓΓp<0 01, Overall analysis of correlated data.
ΓΓΓp<0 001, Overall analysis of correlated data
ßp<0 05, Test for Linear Trend on correlated data
ßßp<0 01, Test for Linear Trend on correlated data
ßßßp<0 001, Test for Linear Trend on correlated data
◊p<0 05, Pairwise comparison of correlated data
◊◊p<0 01, Pairwise comparison of correlated data
◊◊◊p<0 001, Pairwise comparison of correlated data

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 1 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
No Males at Terminal Sacrifice	30	29[a]	30	30	30	30	30
Sacrifice Body Weight (g)[b]	549 6 ‡‡‡ ± 9 0 §§§ N=30	538 8 ± 7 4 N=29	538 0 ± 8 5 N=29[c]	552 4 ± 9 0 N=30	555 8 ± 10 1 N=30	528 3 ± 10 9 N=30	431 4 *** ± 6 4 N=30
Liver Weight (g)[b]	22 3589 ‡‡‡ ± 0 5772 §§§ N=30	22 1417 ± 0 5978 N=29	21 7438 ± 0 5321 N=30	22 4989 ± 0 5467 N=30	21 6185 ± 0 5530 N=30	19 8047 ** ± 0 4568 N=30	16 7909 *** ± 0 3221 N=30
Paired Kidney Weight (g)[b]	4 3499 ‡‡‡ ± 0 0904 §§§ N=30	4 2455 ± 0 0981 N=29	4 4183 ± 0 0754 N=30	4 3794 ± 0 0800 N=30	4 4162 ± 0 0840 N=30	4 2889 ± 0 0936 N=30	3.8589 *** ± 0 1003 N=30
Paired Adrenal Weight (g)[b]	0.0680 ‡‡ ± 0 0021 §§§ N=30	0 0697 ± 0 0024 N=28[d]	0 0686 ± 0 0018 N=30	0 0663 ± 0 0018 N=30	0 0714 ± 0 0030 N=30	0 0649 ± 0 0022 N=30	0 0596 * ± 0 0020 N=30
Spleen Weight (g)[b]	0 8577 ‡ ± 0 0244 §§§ N=30	0.8500 ± 0.0229 N=28[d]	0 8563 ± 0 0190 N=30	0 8894 ± 0 0367 N=30	0.8422 ± 0 0236 N=30	0 8285 ± 0 0222 N=30	0 7572 * ± 0 0283 N=30
Brain Weight (g)[b]	2 0740 ‡ ± 0 0169 §§§ N=30	2.0782 ± 0 0224 N=29	2 0847 ± 0 0207 N=30	2 0993 ± 0 0225 N=30	2 0948 ± 0 0191 N=30	2 0879 ± 0 0199 N=30	2 0089 ± 0 0198 N=30

(continued)

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 2 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[b]							
	0 0174 ‡‡‡	0 0177	0 0174	0 0174	0 0168	0 0162	0 0148 ***
	± 0 0004 §§§	± 0 0005	± 0 0004	± 0 0003	± 0 0004	± 0 0004	± 0 0004
	N=27[e]	N=28[e]	N=30	N=28[e]	N=30	N=28[e]	N=29[e]
Paired Testes Weight (g)[b]							
	3 4819	3 4845	3 4340	3 4627	3 4632	3 4336	3 4313
	± 0 0552	± 0.0561	± 0 0619	± 0 0525	± 0 0496	± 0 0430	± 0 0427
	N=29[d]	N=29	N=30	N=30	N=30	N=30	N=30
Paired Epididymis Weight (g)[b]							
	1 4598	1 4169	1 4125	1.4336	1 4306	1 4072	1 3566
	± 0 0281 §	± 0 0421	± 0 0216	± 0 0278	± 0 0233	± 0 0239	± 0 0241
	N=28[d,f]	N=29	N=30	N=29[d]	N=29[d]	N=30	N=30
Prostate Weight (g)[b]							
	1 0497 ‡‡‡	0 9639	0 9379	0 9684	0 9421	0 9091	0 7299 ***
	± 0 0591 §§§	± 0 0445	± 0 0397	± 0 0493	± 0 0516	± 0 0411	± 0 0360
	N=30	N=29	N=30	N=30	N=30	N=30	N=30
Seminal Vesicles with Coagulating Glands Weight (g)[b]							
	2 2363 ‡‡‡	2 1473	2 3352	2 4993 *	2 3504	2 3295	1.7857 ***
	± 0 0774 §§§	± 0 0873	± 0 0638	± 0 0682	± 0 0600	± 0 0669	± 0 0687
	N=30	N=29	N=30	N=30	N=29[d]	N=30	N=30
Preputial Gland Weight (g)[b]							
	0 2366	0 2423	0 2261	0 2425	0 2348	0 2428	0 2044
	± 0.0148 §	± 0 0133	± 0 0167	± 0 0124	± 0 0145	± 0 0105	± 0 0084
	N=30	N=28[d]	N=30	N=30	N=29[g]	N=30	N=30

(continued)

[redacted]

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 3 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Liver Weight (% sacrifice weight)[b]							
	4 0626 ‡‡ ± 0 0703 N=30	4 1012 ± 0 0802 N=29	4.0040 ± 0 0728 N=29[c]	4 0725 ± 0 0719 N=30	3.8890 ± 0 0658 N=30	3 7518 ** ± 0 0512 N=30	3 8939 ± 0 0508 N=30
Relative Paired Kidney Weight (% sacrifice weight)[b]							
#	0 7917 ¶¶¶ ± 0 0110 ¥¥¥ N=30	0 7910 ± 0 0191 N=29	0 8212 ± 0 0123 N=29[c]	0 7940 ± 0 0101 N=30	0 7955 ± 0.0084 N=30	0 8135 ± 0.0125 N=30	0 9003 ¤¤¤ ± 0 0303 N=30
Relative Paired Adrenal Weight (% sacrifice weight)[b]							
	0 0124 ± 0 0004 §§ N=30	0 0129 ± 0 0004 N=28[d]	0 0128 ± 0.0004 N=29[c]	0 0121 ± 0 0003 N=30	0 0129 ± 0 0006 N=30	0 0123 ± 0 0003 N=30	0 0139 ± 0 0005 N=30
Relative Spleen Weight (% sacrifice weight)[b]							
#	0 1559 ± 0 0032 N=30	0 1587 ± 0 0044 N=28[d]	0 1592 ± 0 0039 N=29[c]	0 1605 ± 0 0052 N=30	0 1521 ± 0 0041 N=30	0 1575 ± 0 0039 N=30	0 1770 ± 0 0083 N=30
Relative Brain Weight (% sacrifice weight)[b]							
	0 3801 ‡‡‡ ± 0 0065 §§§ N=30	0 3877 ± 0 0069 N=29	0 3892 ± 0 0061 N=29[c]	0 3821 ± 0 0060 N=30	0 3804 ± 0 0075 N=30	0 3994 ± 0 0082 N=30	0 4683 *** ± 0 0074 N=30
Relative Pituitary Weight (% sacrifice weight)[b]							
	0 0032 ‡ ± 0 0001 §§ N=27[e]	0 0033 ± 0 0001 N=28[e]	0.0032 ± 0 0001 N=29[c]	0 0032 ± 0 0001 N=28[e]	0.0030 ± 0 0001 N=30	0 0031 ± 0 0001 N=28[e]	0 0034 ± 0 0001 N=29[e]

(continued)

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 4 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Paired Testes Weight (% sacrifice weight)[b]							
	0 6332 ‡‡‡ ± 0 0130 §§§ N=29[d]	0 6485 ± 0 0104 N=29	0 6422 ± 0.0089 N=29[c]	0 6299 ± 0 0109 N=30	0 6285 ± 0 0134 N=30	0 6562 ± 0 0132 N=30	0 7997 *** ± 0 0140 N=30
Relative Paired Epididymis Weight (% sacrifice weight)[b]							
#	0 2651 ¶¶¶ ± 0 0075 ¥¥¥ N=28[d,f]	0 2652 ± 0 0097 N=29	0 2645 ± 0 0043 N=29[c]	0 2613 ± 0.0060 N=29[d]	0 2591 ± 0 0050 N=29[d]	0 2691 ± 0 0069 N=30	0 3152 ¤¤¤ ± 0 0052 N=30
Relative Prostate Weight (% sacrifice weight)[b]							
	0 1919 ± 0 0110 N=30	0 1798 ± 0 0086 N=29	0 1752 ± 0 0073 N=29[c]	0.1770 ± 0 0096 N=30	0 1717 ± 0 0105 N=30	0 1747 ± 0 0090 N=30	0 1692 ± 0.0082 N=30
Relative Seminal Vesicles with Coagulating Glands Weight (% sacrifice weight)[b]							
	0 4081 ± 0 0144 N=30	0 3993 ± 0 0162 N=29	0 4353 ± 0.0130 N=29[c]	0 4536 ± 0 0118 N=30	0 4264 ± 0 0124 N=29[d]	0 4456 ± 0 0149 N=30	0 4136 ± 0 0151 N=30
Relative Preputial Gland Weight (% sacrifice weight)[b]							
	0 0428 ± 0 0025 N=30	0 0449 ± 0 0022 N=28[d]	0 0410 ± 0 0029 N=29[c]	0 0440 ± 0 0022 N=30	0 0426 ± 0 0028 N=29[g]	0 0465 ± 0 0021 N=30	0.0476 ± 0 0020 N=30
Percent Motile Sperm[b]							
#	77 5 ± 2 1 N=30	77 7 ± 3 0 N=29	78 4 ± 1.5 N=30	76 9 ± 1 8 N=30	78 3 ± 2 9 N=30	79 9 ± 1 4 N=30	79 1 ± 1 5 N=30

(continued)

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 5 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Percent Progressively Motile Sperm[b]							
	56 7 ± 2 3 N=30	54 0 ± 3 0 N=29	54 9 ± 2 3 N=30	52 6 ± 2 4 N=30	56 9 ± 2 9 N=30	59 0 ± 2 1 N=30	59 0 ± 2 0 N=30
Epididymal Sperm Concentration (10^6/g)[b]							
	813 14 ± 38 97 N=30	769 90 ± 36 76 N=29	752 69 ± 26 03 N=30	840.46 ± 29 09 N=30	775 56 ± 37 65 N=30	742 48 ± 30 46 N=30	755 52 ± 29 23 N=30
Spermatid Head Concentration (10^6/g)[b]							
	84 26 ± 3 51 N=30	82 58 ± 4 34 N=29	92.28 ± 4 23 N=30	84 79 ± 3 47 N=30	83 31 ± 4 74 N=30	95 61 ± 3 92 N=30	88 23 ± 3.41 N=30
Daily Sperm Production per Testis (10^6/testis/day)[b]							
	31 65 ± 1 57 N=30	31 35 ± 1.87 N=29	34 35 ± 1 52 N=30	31 94 ± 1.43 N=30	31 10 ± 1 83 N=30	35 59 ± 1 44 N=30	32.90 ± 1 30 N=30
Efficiency of Daily Sperm Production (10^6/g testis/day)[b]							
	18 28 ± 0 76 N=30	17 91 ± 0 94 N=29	20 02 ± 0 92 N=30	18.39 ± 0 75 N=30	18 07 ± 1 03 N=30	20 74 ± 0 85 N=30	19 14 ± 0 74 N=30
Percent Abnormal Sperm[b]							
#	3 29 ± 0 92 N=30	1 72 ± 0 21 N=28[h]	2 01 ± 0 24 N=30	2 03 ± 0 28 N=30	5 16 ± 3 27 N=30	2 35 ± 0 71 N=30	1 70 ± 0.16 N=30

(continued)

Table 28 Summary and Statistical Analysis of the F_0 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 6 of 6)

[a]Male 173 was euthanized moribund on study day 57
[b]Reported as the mean ± S E M
[c]Decrease in N is due to the body weight for one male inadvertently not being recorded
[d]Decrease in N is due to one weight being a statistical outlier and therefore it was removed
[e]Decrease in N is due to the pituitary inadvertently not being saved for one or more males
[f]Decrease in N is due to the epididymis weight for one male inadvertently not being recorded
[g]Decrease in N is due to the preputial gland weight for one male inadvertently not being recorded
[h]Sperm morphology could not be evaluated for one male because there were no mature sperm present on the morphology slides
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 001, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 30 Summary and Statistical Analysis of the F_0 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
No Females at Scheduled Sacrifice	30	30	30	30	30	30	30
Sacrifice Body Weight (g)[a]	327 6 ‡‡‡ ± 5 8 §§§ N=30	335 3 ± 4 9 N=30	329 5 ± 4 2 N=30	323 8 ± 6 3 N=29[b]	324 4 ± 4 8 N=30	320 8 ± 4 4 N=30	285 1 *** ± 4 4 N=30
Liver Weight (g)[a]	17 3651 ± 0 5110 N=30	18 0703 ± 0 5598 N=30	17 9488 ± 0 3794 N=30	17 7132 ± 0 6044 N=29[c]	17 6503 ± 0 4612 N=29[d]	17 2499 ± 0 5407 N=30	16 7951 ± 0 5651 N=30
Paired Kidney Weight (g)[a]	2 8449 ‡‡‡ ± 0 0594 §§§ N=30	2 8904 ± 0 0569 N=30	2 9376 ± 0 0398 N=30	2 6866 ± 0 0594 N=30	2 8212 ± 0 0451 N=30	2 7559 ± 0 0487 N=30	2 6336 * ± 0 0453 N=30
Paired Adrenal Weight (g)[a]	0 0950 ‡‡ ± 0 0038 §§§ N=30	0 0921 ± 0 0031 N=29[d]	0 0975 ± 0 0027 N=30	0 0896 ± 0 0030 N=30	0 0960 ± 0 0029 N=30	0 0946 ± 0 0030 N=30	0 0825 * ± 0 0019 N=30
Spleen Weight (g)[a]	0 5905 ‡‡ ± 0 0167 §§§ N=30	0 6078 ± 0 0152 N=30	0 6090 ± 0 0178 N=30	0 6213 ± 0 0183 N=30	0 5739 ± 0 0136 N=30	0 5662 ± 0 0159 N=30	0 5349 ± 0 0168 N=30
Brain Weight (g)[a]	1 8732 ± 0 0192 N=30	1 8558 ± 0 0201 N=30	1 8828 ± 0 0162 N=30	1 8843 ± 0 0210 N=30	1 8753 ± 0 0139 N=30	1 9095 ± 0 0131 N=30	1 8478 ± 0 0207 N=30

(continued)

Table 30 Summary and Statistical Analysis of the F_0 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[a]							
	0 0211 ‡‡‡ ± 0 0008 §§§ N=29[e]	0 0217 ± 0 0006 N=30	0 0237 * ± 0.0008 N=29[e]	0 0202 ± 0 0007 N=30	0 0203 ± 0 0006 N=29[e]	0 0195 ± 0 0006 N=30	0 0156 *** ± 0 0005 N=30
Paired Ovary Weight (g)[a]							
	0 1690 ‡‡‡ ± 0 0059 §§§ N=30	0 1644 ± 0 0056 N=30	0.1694 ± 0.0063 N=30	0 1749 ± 0 0053 N=30	0 1708 ± 0 0044 N=30	0 1589 ± 0 0050 N=30	0 1206 *** ± 0 0031 N=30
Uterus Weight (g)[a]							
	0.7536 ‡‡ ± 0 0260 §§§ N=30	0 6333 * ± 0 0277 N=30	0 7343 ± 0 0473 N=30	0 6744 ± 0 0281 N=30	0 6783 ± 0 0262 N=30	0 6803 ± 0 0252 N=30	0 5752 *** ± 0 0268 N=30
Relative Liver Weight (% sacrifice weight)[a]							
	5.2949 ‡ ± 0 1201 §§§ N=30	5 3652 ± 0 1231 N=30	5 4524 ± 0 1024 N=30	5 4738 ± 0 1300 N=28[b,c]	5 4294 ± 0 1364 N=29[d]	5 3610 ± 0 1354 N=30	5.8661 ** ± 0 1465 N=30
Relative Paired Kidney Weight (% sacrifice weight)[a]							
	0 8703 ‡‡‡ ± 0 0134 §§§ N=30	0 8631 ± 0 0135 N=30	0 8933 ± 0 0112 N=30	0 8380 ± 0 0159 N=29[b]	0 8714 ± 0 0117 N=30	0 8593 ± 0 0099 N=30	0 9254 * ± 0 0124 N=30

(continued)

Table 30 Summary and Statistical Analysis of the F_0 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Paired Adrenal Weight (% sacrifice weight)[a]							
	0 0291 ± 0 0011 N=30	0 0274 ± 0 0008 N=29[d]	0 0298 ± 0 0010 N=30	0 0280 ± 0 0011 N=29[b]	0 0297 ± 0 0009 N=30	0 0295 ± 0 0009 N=30	0 0290 ± 0 0006 N=30
Relative Spleen Weight (% sacrifice weight)[a]							
	0 1807 ± 0 0046 N=30	0 1815 ± 0 0040 N=30	0 1855 ± 0 0056 N=30	0 1920 ± 0 0042 N=29[b]	0 1776 ± 0 0045 N=30	0 1767 ± 0 0046 N=30	0 1874 ± 0 0049 N=30
Relative Brain Weight (% sacrifice weight)[a]							
	0 5769 ‡‡‡ ± 0 0116 §§§ N=30	0 5573 ± 0 0107 N=30	0 5738 ± 0 0079 N=30	0 5859 ± 0.0104 N=29[b]	0 5818 ± 0 0098 N=30	0 5989 ± 0 0098 N=30	0 6516 *** ± 0 0105 N=30
Relative Pituitary Weight (% sacrifice weight)[a]							
	0.0064 ‡‡‡ ± 0 0002 §§§ N=29[e]	0 0065 ± 0 0003 N=30	0 0072 ± 0 0003 N=29[e]	0 0063 ± 0 0003 N=29[b]	0 0063 ± 0 0002 N=29[e]	0 0061 ± 0 0002 N=30	0 0055 * ± 0 0002 N=30
Relative Paired Ovary Weight (% sacrifice weight)[a]							
	0.0518 ‡‡‡ ± 0 0017 §§§ N=30	0 0493 ± 0 0018 N=30	0 0515 ± 0 0019 N=30	0 0542 ± 0 0018 N=29[b]	0 0530 ± 0 0015 N=30	0 0498 ± 0 0017 N=30	0.0424 *** ± 0 0010 N=30
Relative Uterus Weight (% sacrifice weight)[a]							
	0 2332 ± 0 0105 N=30	0 1898 ± 0 0086 N=30	0 2233 ± 0 0140 N=30	0 2139 ± 0 0113 N=29[b]	0 2108 ± 0 0091 N=30	0 2132 ± 0 0085 N=30	0 2024 ± 0 0096 N=30

(continued)

Table 30 Summary and Statistical Analysis of the F_0 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Paired Ovarian Follicle Count[a,f]							
	315 9 ± 41 6 N=10						453 2 Δ ± 26 3 N=10
VAGINAL CYTOLOGY EVALUATION AT NECROPSY[g]							
No Females Evaluated	30	29[h]	30	30	29[h]	29[h]	29[h]
No in Proestrus	11 ££	4 Φ	10	3 Φ	5	3 Φ	1 ΦΦ
% in Proestrus	40 74 ΨΨΨ	13 79	35.71	10 34	18 52	10.34	3 70
No in Estrus	4	4	5	9	5	6	0
% in Estrus	14 81	13.79	17 86	31 03	18.52	20 69	0 00
No in Metestrus	3	4	3	1	3	0	1
% in Metestrus	11.11	13 79	10 71	3 45	11 11	0 00	3 70
No in Diestrus	9 ££	17	10	16	14	20 Φ	25 ΦΦΦ
% in Diestrus	33 33 ΨΨΨ	58 62	35 71	55 17	51 85	68 97	92 59
No Stage Not Determined	2	0	2	1	2	0	2
No No Cells Present	1	0	0	0	0	0	0

(continued)

Table 30 Summary and Statistical Analysis of the F_0 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 5)

---

[a]Reported as the mean ± S E.M
[b]Decrease in N is due to the body weight inadvertently not being recorded for one female
[c]Decrease in N is due to the liver weight for one female being unrealistic
[d]Decrease in N is due to one weight being a statistical outlier and therefore it was removed
[e]Decrease in N is due to the pituitary inadvertently not being saved for one female
[f]Ovarian follicle counts were done for 10 control females and 10 females in the 7500 000 ppm Bisphenol A dose group
[g]For 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, metestrus/estrus and estrus/diestrus 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.
[h]Vaginal smear for one female inadvertently not done
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§§§p<0 001, Test for Linear Trend.
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
££p<0 01, Chi-Square Test
ΨΨΨp<0 001, Cochran-Armitage Test
Φp<0 05, Fisher Exact Test
ΦΦp<0 01, Fisher Exact Test
ΦΦΦp<0 001, Fisher Exact Test
Δp<0 05, Student's t-Test

Table 33 Summary and Statistical Analysis of the F_1 Female Vaginal Opening and the F_1 Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No of Females Evaluated	30	30	30	30	30	30	29[a]
Day of Vaginal Opening[b]							
#	30 5 ¶¶¶ ± 0 3 ¥¥¥ N=30	30 7 ± 0 4 N=30	30 2 ± 0 2 N=30	30 6 ± 0 3 N=30	30 1 ± 0 3 N=30	31 0 ± 0 3 N=30	33 0 ¤¤¤ ± 0 6 N=29
Body Weight (g) on Day of Acquisition[b]							
	102 52 ‡‡‡ ± 2 08 §§§ N=30	105 51 ± 2 10 N=29[c]	98 98 ± 1 41 N=30	106 04 ± 2 60 N=30	99 71 ± 1.50 N=30	102 27 ± 1 79 N=30	92 32 ** ± 2 54 N=29
Adjusted Day of Vaginal Opening[d]							
	30 3 δδδ ± 0 3 λλλ N=30	30 1 ± 0 3 N=30	30 4 ± 0 3 N=30	30 1 ± 0 3 N=30	30 3 ± 0 3 N=30	30 9 ± 0 3 N=30	33 9 φφφ ± 0 3 N=29
No of Males Evaluated	30	30	30	30	30	30	30
Day of Preputial Separation[b]							
	41 9 ‡‡‡ ± 0 3 §§§ N=30	43 2 ± 0 4 N=30	43 1 ± 0 3 N=30	42 2 ± 0 3 N=30	42 8 ± 0 4 N=30	43 6 ** ± 0 4 N=30	45 8 *** ± 0 3 N=30
Body Weight (g) on Day of Acquisition[b]							
	215 70 ‡‡‡ ± 3 10 §§§ N=30	221 28 ± 3 42 N=29[c]	225 06 ± 2 72 N=30	220 57 ± 3 56 N=30	216 69 ± 2 98 N=30	214 19 ± 3 82 N=30	194 02 *** ± 3 33 N=30

(continued)

Table 33 Summary and Statistical Analysis of the F_1 Female Vaginal Opening and the F_1 Male Preputial Separation Data (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Adjusted Day of Preputial Separation[b]							
	41 9 δδδ ± 0 3 λλλ N=30	42 8 ± 0 3 N=30	42 7 ± 0 3 N=30	42 0 ± 0 3 N=30	42 7 ± 0 3 N=30	43 6 φφ ± 0 3 N=30	46 8 φφφ ± 0 4 N=30

[a]Animal 1214 was a male, not a female, as determined by histological examination of the reproductive tissues Therefore, no data is included for this animal

[b]Reported as the mean ± S E M with day being postnatal day

[c]Decrease in N is due to the body weight for one animal inadvertently not being recorded

[d]Reported as the adjusted mean (body weight as covariate) ± S E M , pnd=postnatal day

#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed

¶¶¶p<0 001, Kruskal-Wallis Test

¥¥¥p<0 001, Jonckheere's Test

¤¤¤p<0 001; Mann-Whitney U Test

δδδp<0 001, Analysis of Covariance with body weight on day of acquisition as covariate

λλλp<0 001, Linear Trend Analysis of Covariance with body weight on day of acquisition as covariate

φφp<0 01, Dunnett's Test with body weight on day of acquisition as covariate

φφφp<0 001, Dunnett's Test with body weight on day of acquisition as covariate

‡‡‡p<0 001, ANOVA Test

§§§p<0 001, Test for Linear Trend

**p<0 01, Dunnett's Test.

***p<0 001; Dunnett's Test

Table 34 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]	96 8 ‡‡‡ ± 5 3 §§§ N=30	92 5 ± 5 6 N=30	97 4 ± 5 8 N=30	93 7 ± 5 3 N=30	91 9 ± 4 8 N=30	94 4 ± 5 3 N=30	66 0 *** ± 4 3 N=30
Body Weight (sd 7) (g)[a]	154 4 ‡‡‡ ± 6 7 §§§ N=30	150 7 ± 7 7 N=30	155 7 ± 7 6 N=30	153 3 ± 6 6 N=30	148 2 ± 5 9 N=30	147 5 ± 6 1 N=30	111 5 *** ± 5 1 N=30
Body Weight (sd 14) (g)[a]	213 5 ‡‡‡ ± 6 6 §§§ N=30	211 2 ± 8 3 N=30	215 3 ± 7 7 N=30	212 9 ± 6 6 N=30	207 5 ± 6 1 N=30	203 1 ± 6 5 N=30	158 5 *** ± 4 8 N=30
Body Weight (sd 21) (g)[a]	273 4 ‡‡‡ ± 6 4 §§§ N=30	272 1 ± 8 6 N=30	276 9 ± 7 8 N=30	275 3 ± 6 2 N=30	265.6 ± 5 9 N=30	257 4 ± 6 9 N=30	204 2 *** ± 5 0 N=30
Body Weight (sd 28) (g)[a]	330 7 ‡‡‡ ± 5 6 §§§ N=30	329 8 ± 7 5 N=30	330 8 ± 6 7 N=30	331 3 ± 4 7 N=30	322 2 ± 4 8 N=30	307 3 ± 6 6 N=30	245 0 *** ± 4 6 N=30
Body Weight (sd 35) (g)[a]	374 5 ‡‡‡ ± 5 6 §§§ N=30	374 6 ± 7.6 N=30	375 3 ± 7 2 N=30	379 1 ± 4 5 N=30	368 2 ± 5 0 N=30	348 6 * ± 7 0 N=30	283 7 *** ± 5 1 N=30

(continued)

Table 34 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight (sd 42) (g)[a]							
	410 8 ‡‡‡ ± 6 0 §§§ N=30	412 6 ± 7 3 N=30	412 7 ± 7 1 N=30	418 3 ± 4 8 N=30	405 3 ± 4 8 N=30	381 6 ** ± 7 4 N=30	307 8 *** ± 5 0 N=30
Body Weight (sd 49) (g)[a]							
	439 8 ‡‡‡ ± 6 4 §§§ N=30	441 8 ± 6 9 N=30	439 7 ± 6 9 N=30	448 2 ± 4 9 N=30	433 3 ± 4 8 N=30	408 7 ** ± 7 5 N=30	328 0 *** ± 5 0 N=30
Body Weight (sd 56) (g)[a]							
	458 3 ‡‡‡ ± 6 8 §§§ N=30	460 5 ± 7 1 N=30	457 8 ± 6 9 N=30	471 1 ± 5 1 N=30	456 1 ± 5 1 N=30	428 3 ** ± 8 0 N=30	342 7 *** ± 5 2 N=30
Body Weight (sd 63) (g)[a]							
	482 5 ‡‡‡ ± 7 1 §§§ N=30	484 0 ± 7 9 N=30	480 1 ± 7 6 N=30	495.2 ± 5 4 N=30	479 8 ± 5 5 N=30	450 0 ** ± 8 3 N=30	360 8 *** ± 5 4 N=30
Body Weight (sd 70) (g)[a]							
	494 4 ‡‡‡ ± 8 1 §§§ N=30	495 6 ± 7 8 N=30	492 5 ± 7 5 N=30	504 3 ± 6.9 N=30	487 4 ± 7 2 N=30	459 4 ** ± 8 5 N=30	363 9 *** ± 5 9 N=30
Body Weight (sd 77) (g)[a]							
	501 5 ‡‡‡ ± 8 7 §§§ N=30	500 3 ± 7 5 N=30	501 5 ± 7 3 N=30	517 7 ± 6 3 N=29[b]	497 3 ± 6 8 N=30	468 8 * ± 8 4 N=30	373 6 *** ± 6 0 N=30

(continued)

[redacted]

Table 34 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 3 of 5)

		Bisphenol A (ppm in the feed)						
		0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 84) (g)[a]		519 5 ‡‡‡ ± 9 0 §§§ N=30	520 1 ± 7 9 N=30	549 3 ± 7 6 N=30	535 9 ± 6 9 N=29[b]	517 7 ± 7 2 N=30	485 8 * ± 8 3 N=30	386 1 *** ± 6 1 N=30
Body Weight Change (sd 0 to 7) (g)[a]	#	57 6 ¶¶¶ ± 1 6 ¥¥¥ N=30	58 2 ± 2 6 N=30	58 3 ± 2 0 N=30	59 5 ± 1 7 N=30	56 3 ± 1 4 N=30	53 1 ¤ ± 1 2 N=30	45 5 ¤¤¤ ± 1 1 N=30
Body Weight Change (sd 7 to 14) (g)[a]		59 1 ‡‡‡ ± 1 3 §§§ N=30	60 5 ± 1 1 N=30	59 6 ± 0 9 N=30	59 6 ± 1 0 N=30	59 3 ± 0 9 N=30	55 6 ± 1 2 N=30	47 0 *** ± 1 3 N=30
Body Weight Change (sd 14 to 21) (g)[a]	#	59 9 ¶¶¶ ± 1 5 ¥¥¥ N=30	60 9 ± 1 0 N=30	61 6 ± 1 3 N=30	62 4 ± 1 3 N=30	58 1 ± 2 3 N=30	54 3 ¤¤ ± 1 3 N=30	45 7 ¤¤¤ ± 1 4 N=30
Body Weight Change (sd 21 to 28) (g)[a]		57 3 ‡‡‡ ± 2 3 §§§ N=30	57 7 ± 1 8 N=30	53 9 ± 1 9 N=30	56 0 ± 2 3 N=30	56 6 ± 1.8 N=30	49 9 * ± 1 8 N=30	40 8 *** ± 1 8 N=30

(continued)

Table 34 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 4 of 5)

		Bisphenol A (ppm in the feed)						
		0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 28 to 35) (g)[a]								
	#	43 8 ¶¶¶ ± 1 4 ¥¥¥ N=30	44 8 ± 1 3 N=30	44 5 ± 1 8 N=30	47 8 ± 1 2 N=30	46 0 ± 1 6 N=30	41 3 ± 1 2 N=30	38 7 ¤¤¤ ± 3 6 N=30
Body Weight Change (sd 35 to 42) (g)[a]								
	#	36 3 ¶¶¶ ± 1 6 ¥¥¥ N=30	38 1 ± 1 2 N=30	37 4 ± 1 1 N=30	39 1 ± 1 9 N=30	37 1 ± 1 2 N=30	33 0 ± 1 2 N=30	24 1 ¤¤¤ ± 3 7 N=30
Body Weight Change (sd 42 to 49) (g)[a]								
		29 0 ‡‡‡ ± 1 5 §§§ N=30	29 1 ± 1 3 N=30	27 0 ± 1 4 N=30	29 9 ± 2 1 N=30	28 0 ± 1 6 N=30	27 0 ± 1 5 N=30	20 2 *** ± 1 4 N=30
Body Weight Change (sd 49 to 56) (g)[a]								
		18 5 ‡‡‡ ± 1 1 §§§ N=30	18 7 ± 1 3 N=30	18 1 ± 1 0 N=30	22 9 * ± 1 3 N=30	22 8 * ± 1 3 N=30	19 6 ± 1 1 N=30	14 7 ± 1 1 N=30
Body Weight Change (sd 56 to 63) (g)[a]								
	#	24 2 ¶¶¶ ± 0 9 ¥¥¥ N=30	23 5 ± 1 9 N=30	22 3 ± 1 3 N=30	24 2 ± 1 0 N=30	23 7 ± 0 9 N=30	21 7 ± 1 2 N=30	18 1 ¤¤¤ ± 0 9 N=30
Body Weight Change (sd 63 to 70) (g)[a]								
	#	11 9 ¶¶¶ ± 1 5 ¥¥¥ N=30	11 6 ± 2 3 N=30	12 4 ± 1 0 N=30	9 1 ± 3 5 N=30	7 6 ± 4 0 N=30	9 4 ± 1 6 N=30	3 1 ¤¤¤ ± 2 2 N=30

(continued)

Table 34 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 0 to 70) (g)[a]							
	397 6 ‡‡‡ ± 9 7 §§§ N=30	403 1 ± 7 0 N=30	395 1 ± 5 9 N=30	410 6 ± 9 1 N=30	395 5 ± 7.3 N=30	365 0 * ± 6 7 N=30	297 9 *** ± 6.7 N=30
Body Weight Change (sd 70 to 77) (g)[a]							
	7 1 ± 1 9 N=30	4 7 ± 2 1 N=30	9 1 ± 1 3 N=30	9 9 ± 1 6 N=29[b]	9 9 ± 1 8 N=30	9 4 ± 1 5 N=30	9 6 ± 1 6 N=30
Body Weight Change (sd 77 to 84) (g)[a]							
#	18 1 ± 1 6 ¥ N=30	19 8 ± 2 5 N=30	17.7 ± 1 4 N=30	18 2 ± 1 5 N=29[b]	20 4 ± 2 3 N=30	17 0 ± 1 1 N=30	12 5 ± 1 9 N=30

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the prebreed period
[b]Decrease in N is due to male 1315 being euthanized moribund on study day 72
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡‡‡p<0 001, ANOVA Test
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test.
¶¶¶p<0 001, Kruskal-Wallis Test
¥p<0 05, Jonckheere's Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01, Mann-Whitney U Test.
¤¤¤p<0 001; Mann-Whitney U Test

Table 37 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
No Females on Study	30	30	30	30	30	30	29[a]
Body Weight (sd 0) (g)[b]	87 4 ‡‡‡ ± 4 3 §§§ N=30	89 0 ± 5 0 N=30	87 8 ± 4 8 N=30	88 1 ± 4 6 N=30	85 6 ± 3 9 N=30	86 2 ± 4 4 N=30	62 0 *** ± 3 6 N=29
Body Weight (sd 7) (g)[b]	130 0 ‡‡‡ ± 4 8 §§§ N=30	132 2 ± 5 0 N=30	128 3 ± 5 0 N=30	129 3 ± 4 4 N=30	127 4 ± 3 7 N=30	125 2 ± 4 3 N=30	96 6 *** ± 3 8 N=29
Body Weight (sd 14) (g)[b]	165 6 ‡‡‡ ± 4.0 §§§ N=30	170 1 ± 4 4 N=30	161 6 ± 4 4 N=30	164 9 ± 4 1 N=30	163 4 ± 3 5 N=30	159 1 ± 3 7 N=30	128.8 *** ± 3 2 N=29
Body Weight (sd 21) (g)[b]	192 6 ‡‡‡ ± 4 2 §§§ N=30	198 3 ± 4 2 N=30	190 3 ± 4 6 N=30	192 3 ± 3 7 N=30	191 3 ± 3 4 N=30	184 6 ± 3 8 N=30	152 1 *** ± 2 9 N=29
Body Weight (sd 28) (g)[b]	214 6 ‡‡‡ ± 4 5 §§§ N=30	220 7 ± 4 4 N=30	210 8 ± 4 4 N=30	214.8 ± 4 3 N=30	213 9 ± 3 7 N=30	205 4 ± 3 8 N=30	167 8 *** ± 3 0 N=29
Body Weight (sd 35) (g)[b]	234 7 ‡‡‡ ± 4 8 §§§ N=30	242 1 ± 4 6 N=30	230.4 ± 4 2 N=30	235 3 ± 4 4 N=30	233 3 ± 3 6 N=30	221 9 ± 3 7 N=30	180 5 *** ± 3 1 N=29

(continued)

Table 37 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 42) (g)[b]	248 9 ‡‡‡ ± 5 0 §§§ N=30	258 6 ± 4 5 N=30	244 2 ± 4 3 N=30	250 7 ± 4 4 N=30	251 6 ± 4 1 N=30	235 1 ± 4 1 N=30	191 6 *** ± 3 1 N=29
Body Weight (sd 49) (g)[b]	258 7 ‡‡‡ ± 5 2 §§§ N=30	271 5 ± 4 3 N=30	256 0 ± 4 7 N=30	262 9 ± 4 5 N=30	263 1 ± 4 6 N=30	248 0 ± 4 4 N=30	199 9 *** ± 3 0 N=29
Body Weight (sd 56) (g)[b]	274 0 ‡‡‡ ± 5 2 §§§ N=30	283 5 ± 4 5 N=30	270 3 ± 4 5 N=30	276 7 ± 5 4 N=30	276 0 ± 5 0 N=30	259 2 ± 4 7 N=30	207 0 *** ± 3 2 N=29
Body Weight (sd 63) (g)[b]	286 9 ‡‡‡ ± 5 5 §§§ N=30	299 1 ± 5 1 N=30	286 4 ± 5 2 N=30	293 7 ± 6 2 N=30	290 8 ± 5 7 N=30	271 1 ± 5 6 N=30	213 0 *** ± 3 9 N=29
Body Weight (sd 70) (g)[b]	290 6 ‡‡‡ ± 5 6 §§§ N=30	304 6 ± 5 1 N=30	287 3 ± 4 6 N=30	294 3 ± 5 8 N=30	290 0 ± 5 4 N=30	278 0 ± 5 4 N=30	216 8 *** ± 3 5 N=29
Body Weight (sd 77) (g)[b,c]	284 6 ± 7 8 N=3	310 2 ± 7.7 N=2	371 3 ± N=1	288 1 ± N=1	310 4 ± 8 2 N=2	256 0 ± N=1	211 9 ± N=1

(continued)

Table 37 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 84) (g)[b,c]							
	325 7 ± 9 2 N=2	335 6 ± 3 3 N=2	394 3 ± N=1	± N=0	320 9 ± N=1	271 1 ± N=1	228 0 ± N=1
Body Weight Change (sd 0 to 7) (g)[b]							
	42.6 ‡‡‡ ± 1 3 §§§ N=30	43 2 ± 0 9 N=30	40 5 ± 0 9 N=30	41 2 ± 1 0 N=30	41 8 ± 0 8 N=30	39 0 * ± 0 9 N=30	34 7 *** ± 0 7 N=29
Body Weight Change (sd 7 to 14) (g)[b]							
	35 7 ± 1 8 § N=30	37 9 ± 1 2 N=30	33 3 ± 1 4 N=30	35 6 ± 1 4 N=30	36 0 ± 1 3 N=30	34 0 ± 1 3 N=30	32 1 ± 1 1 N=29
Body Weight Change (sd 14 to 21) (g)[b]							
	27 0 ‡ ± 1 4 §§ N=30	28 2 ± 1 1 N=30	28 7 ± 1 4 N=30	27 4 ± 1 5 N=30	27 9 ± 1 1 N=30	25 5 ± 1 0 N=30	23 3 ± 1.2 N=29
Body Weight Change (sd 21 to 28) (g)[b]							
	22 0 ‡‡‡ ± 1 3 §§§ N=30	22 4 ± 1 1 N=30	20.5 ± 1.2 N=30	22 6 ± 1 2 N=30	22 6 ± 1 0 N=30	20 8 ± 1 1 N=30	15 7 *** ± 0 9 N=29
Body Weight Change (sd 28 to 35) (g)[b]							
	20 1 ‡‡‡ ± 1 3 §§§ N=30	21 4 ± 1 2 N=30	19 6 ± 1 4 N=30	20 5 ± 1 2 N=30	19 4 ± 1 2 N=30	16.5 ± 1 1 N=30	12 6 *** ± 0 8 N=29

(continued)

Table 37 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 35 to 42) (g)[b]							
	14 2 ‡‡‡ ± 1 2 §§§ N=30	16 5 ± 1 0 N=30	13 8 ± 1 0 N=30	15 4 ± 1 1 N=30	18 3 * ± 1 3 N=30	13 1 ± 0 9 N=30	11 1 ± 0 8 N=29
Body Weight Change (sd 42 to 49) (g)[b]							
	9 8 ± 1 2 § N=30	12.9 ± 1 4 N=30	11 8 ± 1 5 N=30	12 2 ± 1 2 N=30	11 5 ± 1 2 N=30	12 9 ± 0 9 N=30	8 3 ± 0 9 N=29
Body Weight Change (sd 49 to 56) (g)[b]							
	15 3 ‡ ± 2.1 §§ N=30	12 0 ± 1 9 N=30	14 3 ± 1 7 N=30	13 8 ± 2 0 N=30	12 8 ± 1 6 N=30	11 2 ± 1 7 N=30	7 1 ** ± 1 2 N=29
Body Weight Change (sd 56 to 63) (g)[b]							
	13 0 ‡‡‡ ± 1 6 §§§ N=30	15 6 ± 1 7 N=30	16 0 ± 2 0 N=30	16 9 ± 1 8 N=30	14 8 ± 1 7 N=30	12 0 ± 1 9 N=30	6 0 * ± 2 1 N=29
Body Weight Change (sd 63 to 70) (g)[b]							
	3 7 ± 2 0 N=30	5 5 ± 2 4 N=30	0.9 ± 2.5 N=30	0 6 ± 3 0 N=30	-0 7 ± 2 1 N=30	6 9 ± 2 2 N=30	3 7 ± 2 0 N=29
Body Weight Change (sd 0 to 70) (g)[b]							
	203.2 ‡‡‡ ± 5.5 §§§ N=30	215 6 ± 5 2 N=30	199.4 ± 5 5 N=30	206 2 ± 6 5 N=30	204 4 ± 5 9 N=30	191 8 ± 5 0 N=30	154 8 *** ± 4 8 N=29

(continued)

Table 37 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight Change (sd 70 to 77) (g)[b,c]							
	9 9 ± 3 6 N=3	6 5 ± 1 7 N=2	14 7 ± N=1	28 6 ± N=1	20 5 ± 4 4 N=2	18 9 ± N=1	13 0 ± N=1
Body Weight Change (sd 77 to 84) (g)[b,c]							
	34 0 ± 14 6 N=2	25 4 ± 4 4 N=2	23 0 ± N=1	± N=0	18 8 ± N=1	15 1 ± N=1	16 2 ± N=1

[a]Animal 1214 was a male, not a female, as determined by histological examination of the reproductive tissues Therefore, no data is included for this animal
[b]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the prebreed period
[c]Includes all females that were not found sperm and/or plug positive Statistical analyses were not performed on these endpoints since not all females were represented
‡p<0 05, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test

[redacted]

Table 41 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During Gestation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No Sperm Positive Pregnant Females	26	28	29	27	27	26	27
Body Weight (gd 0) (g)[a]	285 7 ‡‡‡ ± 5 7 §§§ N=26	299 0 ± 5 2 N=28	282.1 ± 4 0 N=29	288 9 ± 5 9 N=27	284 7 ± 5 2 N=27	269 1 ± 5 8 N=26	215 4 *** ± 3.3 N=27
Body Weight (gd 7) (g)[a]	315 5 ‡‡‡ ± 6 1 §§§ N=26	327 9 ± 4 9 N=28	312 1 ± 4 2 N=29	319 5 ± 6 1 N=27	312 4 ± 5 0 N=27	294 8 * ± 5 8 N=26	231.9 *** ± 4 3 N=27
Body Weight (gd 14) (g)[a]	346 6 ‡‡‡ ± 6.7 §§§ N=26	360 6 ± 5 4 N=28	341 7 ± 4 3 N=29	347 4 ± 6 1 N=27	342 3 ± 5 5 N=27	321 5 * ± 6 4 N=26	255.8 *** ± 4 3 N=27
Body Weight (gd 20) (g)[a]	417 9 ‡‡‡ ± 8.1 §§§ N=26	433 8 ± 6.8 N=27[b]	415 0 ± 5.2 N=29	415 1 ± 5 9 N=27	412 7 ± 6 2 N=27	395 6 ± 7 3 N=26	312.5 *** ± 5 8 N=26[c]
Body Weight Change (gd 0 to 7) (g)[a]	29 8 ‡‡‡ ± 1 5 §§§ N=26	28 9 ± 1 9 N=28	30 0 ± 1 6 N=29	30 6 ± 1 9 N=27	27 7 ± 1 2 N=27	25 8 ± 2 1 N=26	16 5 *** ± 2.6 N=27

(continued)

Table 41 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During Gestation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (gd 7 to 14) (g)[a]							
#	31 2 ¶¶¶ ± 1 4 ¥¥¥ N=26	32 7 ± 1 0 N=28	29 6 ± 1 4 N=29	27 9 ± 1 1 N=27	29 9 ± 1 3 N=27	26 7 ¤ ± 1 4 N=26	23 9 ¤¤¤ ± 2.7 N=27
Body Weight Change (gd 14 to 20) (g)[a]							
#	71 2 ¶¶¶ ± 2 5 ¥¥¥ N=26	74 1 ± 2 1 N=27[b]	73 3 ± 2 2 N=29	67 7 ± 4 5 N=27	70 4 ± 1 8 N=27	74 1 ± 2 1 N=26	56 0 ¤¤¤ ± 2 4 N=26[c]
Body Weight Change (gd 0 to 20) (g)[a]							
	132 2 ‡‡‡ ± 3 8 §§§ N=26	135 9 ± 3 7 N=27[b]	132 9 ± 3 6 N=29	126 2 ± 4 7 N=27	128 0 ± 2 7 N=27	126 5 ± 3 0 N=26	97 6 *** ± 3 8 N=26[c]

[a]Reported as the mean ± S E M , gd=gestational day

[b]Decrease in N is due to female 1256 being in the process of delivering at the time of weighing on gestatonal day 20 and therefore the body weight was not taken

[c]Decrease in N is due to female 1204 being euthanized moribund on gestational day 15 (study day 87)

#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed

‡‡‡p<0 001, ANOVA Test

§§§p<0 001, Test for Linear Trend

*p<0 05, Dunnett's Test

***p<0 001, Dunnett's Test

¶¶¶p<0 001, Kruskal-Wallis Test

¥¥¥p<0 001, Jonckheere's Test

¤p<0 05, Mann-Whitney U Test

¤¤¤p<0 001, Mann-Whitney U Test

Table 44 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During Lactation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750 000	7500.000
No Females with Litters on Postnatal Day 0	27[a]	30	30	26[b]	27	26	27[c]
Body Weight (pnd 0) (g)[d]	326 7 ‡‡‡ ± 5 4 §§§ N=27	337 4 ± 4 6 N=30	321 3 ± 5 4 N=30	320 4 ± 5 4 N=26	323 6 ± 5 8 N=27	298.3 ** ± 5 8 N=26	243 3 *** ± 4 1 N=27
Body Weight (pnd 4) (g)[d]	336 3 ‡‡‡ ± 5 8 §§§ N=27	352 2 ± 4.3 N=30	328 9 ± 4 7 N=30	331 1 ± 4 5 N=26	331 0 ± 5 5 N=27	310 8 ** ± 5 9 N=26	245 9 *** ± 3 9 N=26[e]
Body Weight (pnd 7) (g)[d]	344 8 ‡‡‡ ± 5 6 §§§ N=27	359 0 ± 4 4 N=30	338 7 ± 4 6 N=30	342 2 ± 4 2 N=26	343 1 ± 5 1 N=27	322 9 * ± 6 2 N=26	262 2 *** ± 4 4 N=26
Body Weight (pnd 14) (g)[d]	357 7 ‡‡‡ ± 5 9 §§§ N=27	362 8 ± 4 6 N=30	351 7 ± 4 7 N=30	349.5 ± 4 9 N=26	348 4 ± 4 7 N=27	331 6 ** ± 6 1 N=26	276 7 *** ± 4 5 N=26
Body Weight (pnd 21) (g)[d]	341 7 ‡‡‡ ± 6 0 §§§ N=27	349 0 ± 4 9 N=30	337 0 ± 4 2 N=30	337 2 ± 4.6 N=26	337 0 ± 4.6 N=27	324 4 ± 5 3 N=26	287 6 *** ± 4 8 N=26

(continued)

Table 44 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During Lactation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (pnd 0 to 4) (g)[d]	9.6 ‡ ± 2.1 §§ N=27	14 8 ± 2 0 N=30	7 7 ± 2 7 N=30	10 8 ± 3 1 N=26	7 4 ± 2 9 N=27	12 5 ± 2 4 N=26	1 8 ± 2 2 N=26[e]
Body Weight Change (pnd 4 to 7) (g)[d]	8 5 ‡‡ ± 1 7 §§§ N=27	6 8 ± 1 7 N=30	9 7 ± 1 3 N=30	11 1 ± 1 6 N=26	12 1 ± 1 7 N=27	12 1 ± 1 7 N=26	16 3 ** ± 1 9 N=26
Body Weight Change (pnd 7 to 14) (g)[d]	12 9 ± 2 2 N=27	3 9 ± 3 4 N=30	13.0 ± 2 5 N=30	7 3 ± 3 4 N=26	5.3 ± 3 0 N=27	8 7 ± 3 9 N=26	14 5 ± 2 4 N=26
Body Weight Change (pnd 14 to 21) (g)[d]	-16 0 ‡‡‡ ± 4 1 §§§ N=27	-13 8 ± 3 4 N=30	-14 7 ± 2 5 N=30	-12 3 ± 3 3 N=26	-11 4 ± 3 3 N=27	-7 3 ± 3 6 N=26	10 9 *** ± 2 7 N=26
Body Weight Change (pnd 0 to 21) (g)[d]	15 1 ‡‡‡ ± 3 8 §§§ N=27	11.6 ± 3.9 N=30	15 8 ± 3 1 N=30	16 9 ± 4 0 N=26	13 5 ± 4 2 N=27	26 1 ± 3 2 N=26	43 4 *** ± 3 1 N=26

[a]Female 1238 was pregnant but died during delivery
[b]Female 1292 was pregnant but did not deliver a litter (had implant sites only)
[c]Female 1204 was pregnant but was euthanized moribund on gestational day 15 (study day 87)
[d]Reported as the mean ± S E M , pnd=postnatal day
[e]Decrease in N is due to the entire litter of female 1170 being dead or euthanized moribund on or before postnatal day 3
‡p<0 05, ANOVA Test ‡‡p<0 01, ANOVA Test ‡‡‡p<0 001, ANOVA Test
§§p<0 01, Test for Linear Trend §§§p<0.001, Test for Linear Trend
*p<0 05, Dunnett's Test **p<0 01; Dunnett's Test ***p<0 001, Dunnett's Test

Table 47 Summary and Statistıcal Analysıs of the F_1 Reproductıve and Lactational Indexes for the F_2 Litters (page 1 of 5)

	Bısphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
No Anımals on Study							
Males	30	30	30	30	30	30	30
Females	30	30	30	30	30	30	29[a]
No Females Paıred							
	30	30	30	30	30	30	29
No of Females that Mated							
	30	30	30	30	29	29	29
Matıng Index (no females that mated/no females paired)							
	100 0	100 0	100 0	100 0	96 7	96 7	100 0
No of Pregnant Females							
	28	30	30	27	27	26	28
Fertılıty Index (no pregnant females/no females that mated)							
	93 3	100 0	100.0	90 0	93.1	89 7	96 6
No of Females wıth Lıve Lıtters (pnd 0)							
	28	30	30	26[b]	27	26	27[c]
Gestatıonal Index (no females with live lıtters/no females pregnant)							
	100.0	100 0	100 0	96 3	100 0	100 0	100 0

(continued)

Table 47. Summary and Statistical Analysis of the F_1 Reproductive and Lactational Indexes for the F_2 Litters (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
No Males Paired							
	30	30	30	29[d]	30	30	29[e]
No Males that Mated							
	30	30	30	29	29	29	29
Mating Index (no males that mated/no males paired)							
	100 0	100 0	100 0	100.0	96 7	96 7	100 0
No Males Siring Litters							
	28	30	30	27	27	26	28
Fertility Index (no males siring litters/no males that mated)							
	93 3	100 0	100 0	93 1	93 1	89 7	96 6
Pregnancy Index (no pregnant females/no. males that mated)							
	93 3	100 0	100 0	93 1	93 1	89 7	96 6
Days until Sperm Positive (days)[f,g]							
#	3 0 ± 0 4 N=28	3 2 ± 0 3 N=28	2 7 ± 0 2 N=29	3 1 ± 0 4 N=30	3 1 ± 0 4 N=29	2 8 ± 0 3 N=29	2 7 ± 0 2 N=28
Gestational Length (days)[f,h]							
	21 8 ± 0.1 N=26	22 0 ± 0 1 N=28	21 9 ± 0 1 N=29	22 0 ± 0 1 N=26	21 9 ± 0 1 N=27	22 0 ± 0 1 N=26	21 8 ± 0 1 N=26

(continued)

Table 47 Summary and Statistical Analysis of the F_1 Reproductive and Lactational Indexes for the F_2 Litters (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
No of Live Litters							
Postnatal Day 0	28[i]	30	30	26	27	26	27
Postnatal Day 4	27	30	30	26	27	26	26[j]
Postnatal Day 7	27	30	30	26	27	26	26
Postnatal Day 14	27	30	30	26	27	26	26
Postnatal Day 21	27	30	30	26	27	26	26
No Implantation Sites per Litter[f]							
#	15 86 ¶¶¶	16.33	15 13	14.85	15 33	16 00	11 93 ¤¤¤
	± 0 44 ¥¥¥	± 0.46	± 0 64	± 0 79	± 0.39	± 0 38	± 0.43
	N=28	N=30	N=30	N=27	N=27	N=26	N=28
Percent Postimplantation Loss per Litter[f]							
	9 35	9 11	7 59	6 44	7 04	7.37	11.08
	± 1 83	± 1 51	± 1 97	± 1 70	± 1 44	± 1 98	± 2 21
	N=27	N=30	N=30	N=26	N=27	N=26	N=27
Number of Live Pups on Postnatal Day 0[f]							
	14 6 ‡‡‡	14 9	14 3	14 7	14 3	14 9	10 8 ***
	± 0 6 §§§	± 0 4	± 0 7	± 0 7	± 0 4	± 0.5	± 0 5
	N=27	N=30	N=30	N=26	N=27	N=26	N=27
Number of Dead Pups on Postnatal Day 0[f]							
#	0 3	0 2	0.2	0 0	0 2	0 1	0.3
	± 0 1	± 0 1	± 0 1	± 0 0	± 0 1	± 0 1	± 0 2
	N=27	N=30	N=30	N=26	N=27	N=26	N=27
Total Number of Pups on Postnatal Day 0[f]							
	14 9 ‡‡‡	15 1	14 5	14.7	14.5	15 0	11.1 ***
	± 0.6 §§§	± 0.5	± 0.7	± 0.7	± 0.5	± 0 5	± 0.5
	N=27	N=30	N=30	N=26	N=27	N=26	N=27

(continued)

Table 47 Summary and Statistical Analysis of the F_1 Reproductive and Lactational Indexes for the F_2 Litters (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Stillbirth Index (no dead on pnd 0/total no on pnd 0)[f]							
#	1 7 ± 0 8 N=27	1 0 ± 0 5 N=30	1 9 ± 0 8 N=30	0 0 ± 0 0 N=26	1 4 ± 0 6 N=27	0 8 ± 0.4 N=26	2 9 ± 1 7 N=27
Live Birth Index (no live on pnd 0/total no on pnd 0)[f]							
#	98.3 ± 0 8 N=27	99 0 ± 0 5 N=30	98 1 ± 0 8 N=30	100 0 ± 0 0 N=26	98 6 ± 0 6 N=27	99 2 ± 0 4 N=26	97 1 ± 1 7 N=27
4 Day Survival Index (no surviving 4 days/no live on pnd 0)[f]							
#	98 6 ± 0 5 N=27	99 2 ± 0 4 N=30	95 6 ± 1 4 N=30	98 6 ± 0 6 N=26	98 9 ± 0 5 N=27	99 6 ± 0 3 N=26	93 9 ± 3 7 N=27
7 Day Survival Index (no surviving 7 days/no live on pnd 4)[f]							
#	99 3 ± 0 5 N=27	100 0 ± 0 0 N=30	100.0 ± 0 0 N=30	100 0 ± 0 0 N=26	98 9 ± 0 6 N=27	100 0 ± 0 0 N=26	99 6 ± 0 4 N=26
14 Day Survival Index (no surviving 14 days/no live on pnd 7)[f]							
#	100 0 ± 0 0 N=27	99 7 ± 0 3 N=30	99 7 ± 0 3 N=30	100 0 ± 0.0 N=26	98 8 ± 1 2 N=27	100 0 ± 0 0 N=26	99.5 ± 0 5 N=26
21 Day Survival Index (no surviving 21 days/no live on pnd 14)[f]							
#	100 0 ± 0 0 N=27	100 0 ± 0 0 N=30	100 0 ± 0 0 N=30	99 6 ± 0 4 N=26	100 0 ± 0 0 N=27	100 0 ± 0 0 N=26	100 0 ± 0 0 N=26

(continued)

Table 47 Summary and Statistical Analysis of the F_1 Reproductive and Lactational Indexes for the F_2 Litters (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750.000	7500.000
Lactational Index (no surviving 21 days/no live on pnd 4)[f]							
#	99 3 ± 0 5 N=27	99.7 ± 0 3 N=30	99 7 ± 0.3 N=30	99 6 ± 0.4 N=26	97.8 ± 1 5 N=27	100 0 ± 0 0 N=26	99 1 ± 0 7 N=26

[a]Animal 1214 was a male, not a female, as determined by histological examination of the reproductive tissues Therefore, no data is included for this animal
[b]Female 1292 had implant sites only
[c]Female 1204 was euthanized moribund on gestational day 15 She was included as a female that mated and was pregnant and her number of implant sites was also included, but she was not included for any other reproductive or lactational indexes since she did not have the opportunity to deliver
[d]Male 1315 was euthanized moribund on study day 72
[e]Male 1379 was not mated because there were only 29 females available
[f]Reported as the mean ± S E M , pnd=postnatal day All indexes are the average percent per litter
[g]Days until sperm positive could only be calculated for those females for which sperm were detected in the vaginal smear
[h]Gestational length could not be calculated for females that were pregnant, but for which sperm were never detected in the vaginal smear.
[i]Female 1238 died during delivery She delivered 3 live pups and 1 dead pup and had 11 retained full term dead fetuses in utero She was included as a pregnant female with a live litter and her number of implant sites was also included, but she was not included for any other reproductive or lactational indexes
[j]The entire litter for female 1170 was dead, missing and presumed dead or euthanized moribund on or before postnatal day 3
[#]Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
¶¶¶p<0 001, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤¤¤p<0 001, Mann-Whitney U Test
‡‡‡p<0 001, ANOVA Test
§§§p<0 001; Test for Linear Trend
***p<0 001, Dunnett's Test

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 1 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No of Live Litters							
Postnatal Day 0	28[a]	30	30	26	27	26	27
Postnatal Day 4	27	30	30	26	27	26	26[b]
Postnatal Day 7	27	30	30	26	27	26	26
Postnatal Day 14	27	30	30	26	27	26	26
Postnatal Day 21	27	30	30	26	27	26	26
Average Number of Pups per Litter (pnd 0)[c]							
	14 6 ‡‡‡	14 9	14 3	14 7	14 3	14 9	10 8 ***
	± 0 6 §§§	± 0 4	± 0 7	± 0 7	± 0 4	± 0 5	± 0 5
	N=27	N=30	N=30	N=26	N=27	N=26	N=27
Average Number of Pups per Litter (pnd 4)[c]							
	14 4 ‡‡‡	14 8	13 6	14 5	14 1	14 8	10.3 ***
	± 0 5 §§§	± 0 4	± 0 6	± 0 7	± 0 4	± 0 5	± 0 7
	N=27	N=30	N=30	N=26	N=27	N=26	N=27
Average Number of Pups per Litter (pnd 7)[c]							
#	9 8 ¶	9 9	9 5	9 6	9 9	10 0 ¤	9 2
	± 0 2	± 0 1	± 0.3	± 0 2	± 0 1	± 0 0	± 0 3
	N=27	N=30	N=30	N=26	N=27	N=26	N=26
Average Number of Pups per Litter (pnd 14)[c]							
#	9 8	9 9	9 5	9 6	9 8	10 0	9 1
	± 0 2	± 0 1	± 0 3	± 0 2	± 0 2	± 0 0	± 0.4
	N=27	N=30	N=30	N=26	N=27	N=26	N=26
Average Number of Pups per Litter (pnd 21)[c]							
#	9 8	9 9	9 5	9 6	9 8	10 0	9 1
	± 0 2	± 0 1	± 0 3	± 0 2	± 0 2	± 0 0	± 0 4
	N=27	N=30	N=30	N=26	N=27	N=26	N=26

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 2 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Average Male Anogenital Distance (mm) per Litter (pnd 0)[c]							
#	1 98 ± 0 01 N=27	2 00 ± 0 02 N=30	1 98 ± 0 02 N=30	1 97 ± 0.01 N=26	1 95 ± 0 01 N=27	1 96 ± 0 02 N=26	2 00 ± 0 01 N=27
Average Adjusted Male Anogenital Distance (mm) per Litter (pnd 0)[d]							
	1 96 ± 0 02 N=27	1 99 ± 0 02 N=30	1 98 ± 0 02 N=30	1 97 ± 0 02 N=26	1 95 ± 0 02 N=27	1.96 ± 0 02 N=26	2 00 ± 0 02 N=27
Average Female Anogenital Distance (mm) per Litter (pnd 0)[c]							
	0 95 ‡‡ ± 0 01 N=27	0 98 * ± 0 01 N=30	0 98 ** ± 0 01 N=30	0 98 * ± 0 01 N=26	0 97 ± 0 01 N=27	0.99 ** ± 0 01 N=26	0 96 ± 0.01 N=26[e]
Average Adjusted Female Anogenital Distance (mm) per Litter (pnd 0)[d]							
	0 95 δδ ± 0 01 N=27	0 98 φ ± 0 01 N=30	0 98 φφ ± 0 01 N=30	0 98 φ ± 0 01 N=26	0 97 ± 0 01 N=27	0 99 φφ ± 0 01 N=26	0.96 ± 0.01 N=26[e]

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 3 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4.500	75 000	750 000	7500 000
Average Pup Body Weight (g) per Litter (pnd 0)[c]							
	6 12 ± 0 11 N=27	6.29 ± 0 09 N=30	6 12 ± 0 15 N=30	6.29 ± 0 08 N=26	6 21 ± 0 12 N=27	6 20 ± 0 09 N=26	6 22 ± 0 10 N=27
Average **Male** Body Weight (g) per Litter (pnd 0)[c]							
	6 28 ± 0 11 N=27	6 51 ± 0 11 N=30	6 28 ± 0 16 N=30	6 45 ± 0 08 N=26	6 40 ± 0 12 N=27	6 42 ± 0 10 N=26	6 38 ± 0 10 N=27
Average **Female** Body Weight (g) per Litter (pnd 0)[c]							
	5.97 ± 0 11 N=27	6 10 ± 0 09 N=30	5 94 ± 0 15 N=30	6 13 ± 0 08 N=26	6 01 ± 0 12 N=27	6 00 ± 0 08 N=26	5 99 ± 0.10 N=26[e]
Average Pup Body Weight (g) per Litter (pnd 4)[c]							
	10 09 ± 0 25 § N=27	10 29 ± 0 25 N=30	10 17 ± 0.34 N=30	10 00 ± 0 20 N=26	9 79 ± 0 26 N=27	9 97 ± 0 27 N=26	9 50 ± 0 19 N=26
Average **Male** Body Weight (g) per Litter (pnd 4)[c]							
	10 35 ± 0 26 § N=27	10 59 ± 0 27 N=30	10 39 ± 0 35 N=30	10.11 ± 0 22 N=26	10 05 ± 0.25 N=27	10 22 ± 0 28 N=26	9 62 ± 0 20 N=26
Average **Female** Body Weight (g) per Litter (pnd 4)[c]							
	9 83 ± 0 25 N=27	10 05 ± 0.24 N=30	9 97 ± 0.33 N=30	9.90 ± 0.21 N=26	9 51 ± 0.26 N=27	9 72 ± 0 27 N=26	9 34 ± 0.19 N=25[e]

[redacted]

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 4 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0.300	4 500	75 000	750 000	7500.000
Average Pup Body Weight (g) per Litter (pnd 7)[c]							
	16 00 ‡‡‡ ± 0 35 §§§ N=27	16 37 ± 0 28 N=30	16 10 ± 0 45 N=30	15 59 ± 0 27 N=26	15 17 ± 0 37 N=27	15 66 ± 0 39 N=26	13 58 *** ± 0.30 N=26
Average **Male** Body Weight (g) per Litter (pnd 7)[c]							
	16 40 ‡‡‡ ± 0 35 §§§ N=27	16 80 ± 0 30 N=30	16 34 ± 0 44 N=30	15 73 ± 0 30 N=26	15 55 ± 0 36 N=27	16 02 ± 0 42 N=26	13 70 *** ± 0 31 N=26
Average **Female** Body Weight (g) per Litter (pnd 7)[c]							
	15 62 ‡‡‡ ± 0 36 §§§ N=27	16 01 ± 0 29 N=30	15 83 ± 0 46 N=30	15 46 ± 0.29 N=26	14 78 ± 0 39 N=27	15 32 ± 0 38 N=26	13 47 *** ± 0 31 N=25[e]
Average Pup Body Weight (g) per Litter (pnd 14)[c]							
	32 60 ‡‡‡ ± 0 46 §§§ N=27	33 20 ± 0 42 N=30	33 07 ± 0 73 N=30	31 82 ± 0.47 N=26	31 43 ± 0 58 N=27	31 45 ± 0 65 N=26	26.13 *** ± 0.64 N=26
Average **Male** Body Weight (g) per Litter (pnd 14)[c]							
	33 22 ‡‡‡ ± 0 46 §§§ N=27	33 91 ± 0 43 N=30	33 45 ± 0 73 N=30	32.03 ± 0 49 N=26	31 95 ± 0 61 N=27	32 00 ± 0 67 N=26	26 49 *** ± 0 66 N=26
Average **Female** Body Weight (g) per Litter (pnd 14)[c]							
	31 97 ‡‡‡ ± 0 47 §§§ N=27	32 60 ± 0 44 N=30	32 61 ± 0.73 N=30	31 64 ± 0 50 N=26	30 84 ± 0 60 N=27	30 98 ± 0 67 N=26	25.83 *** ± 0 64 N=25[e]

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 5 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Average Pup Body Weight (g) per Litter (pnd 21)[c]							
#	48 48 ¶¶¶ ± 0 67 ¥¥¥ N=27	47 45 ± 0 63 N=30	47 96 ± 1 30 N=30	46 31 ¤ ± 0 69 N=26	45 05 ¤¤ ± 0 77 N=27	46 33 ¤ ± 0 89 N=26	38 82 ¤¤¤ ± 0 98 N=26
Average **Male** Body Weight (g) per Litter (pnd 21)[c]							
	49 72 ‡‡‡ ± 0 69 §§§ N=27	48 70 ± 0 70 N=30	48 67 ± 1 28 N=30	46 59 ± 0 73 N=26	45 98 * ± 0 86 N=27	47 48 ± 0 92 N=26	39 81 *** ± 1 06 N=26
Average **Female** Body Weight (g) per Litter (pnd 21)[c]							
#	47 09 ¶¶¶ ± 0 64 ¥¥¥ N=27	46 37 ± 0 67 N=30	47 13 ± 1 32 N=30	46 01 ± 0 75 N=26	44 03 ¤¤ ± 0 74 N=27	45 31 ± 0.91 N=26	37 81 ¤¤¤ ± 0 91 N=25[e]
Percent Male Pups per Litter (pnd 0)[c]							
	51 8 ± 2 8 §§ N=27	47 9 ± 2 2 N=30	53 5 ± 3 1 N=30	49.3 ± 2 6 N=26	49 1 ± 2 7 N=27	48 2 ± 3 2 N=26	58 5 ± 3.3 N=27
Percent Male Pups per Litter (pnd 4)[c]							
	51 3 ± 2 9 §§ N=27	47 7 ± 2 2 N=30	53 9 ± 3 1 N=30	49 5 ± 2 7 N=26	49 4 ± 2 9 N=27	48 4 ± 3 2 N=26	58 7 ± 3 7 N=26
Percent Male Pups per Litter (pnd 7)[c]							
#	50 6 ¶ ± 1 7 N=27	48.3 ± 1 1 N=30	53 4 ± 2 1 N=30	51.1 ± 1 8 N=26	49.0 ± 1 4 N=27	48 1 ± 1 8 N=26	56.9 ¤ ± 3 4 N=26

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 6 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Percent Male Pups per Litter (pnd 14)[c]							
#	50 6 ¶ ± 1.7 N=27	48 2 ± 1 1 N=30	53 6 ± 2 1 N=30	50 7 ± 1 9 N=26	49 0 ± 1 4 N=27	48 1 ± 1 8 N=26	56 6 ± 3 4 N=26
Percent Male Pups per Litter (pnd 21)[c]							
#	50 6 ¶ ± 1 7 N=27	48 2 ± 1 1 N=30	53 6 ± 2 1 N=30	50 9 ± 1 9 N=26	49 0 ± 1 4 N=27	48 1 ± 1 8 N=26	56 6 ± 3 4 N=26
No of Nipples per Animal[f]							
	0 00 ± 0 00 N=133	0 00 ± 0 00 N=143	0 00 ± 0 00 N=152	0 00 ± 0 00 N=128	0 01 ± 0 01 N=130	0 00 ± 0 00 N=125	0 00 ± 0 00 N=134
Percent with One or More Nipples							
	0 00	0 00	0 00	0 00	0 77	0 00	0 00
No of Areolae per Animal[f]							
	0 05 ± 0 03 N=133	0 06 ± 0 03 N=143	0 09 ± 0 06 N=152	0 04 ± 0 03 N=128	0 02 ± 0 01 N=130	0.05 ± 0.03 N=125	0 05 ± 0 03 N=134
Percent with One or More Areolae							
	2 26	2 10	3 95	1 57	1 54	2 40	2 26

(continued)

Table 48 Summary and Statistical Analysis of the F_2 Litter Size, F_2 Pup Anogenital Distance, F_2 Pup Body Weights, Percent F_2 Males and F_2 Male Nipple Evaluations During Lactation (page 7 of 7)

---

[a]Female 1238 died during delivery She delivered 3 live pups and 1 dead pup and had 11 retained full term dead fetuses in utero
[b]The entire litter for female 1170 was dead, missing and presumed dead or euthanized moribund on or before postnatal day 3
[c]Reported as the mean ± S E M , pnd=postnatal day
[d]Reported as the adjusted mean (body weight as covariate) ± S E M , pnd=postnatal day
[e]Decrease in N is due to one female having a litter of all male pups
[f]Reported as the mean ± S.E M (adjusted for intralitter correlations)
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶p<0 05, Kruskal-Wallis Test
¶¶¶p<0 001, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test
δδδp<0 001, Analysis of Covariance with body weight on postnatal day 0 as covariate
φp<0 05, Dunnett's Test with body weight on postnatal day 0 as covariate
φφp<0 01, Dunnett's Test with body weight on postnatal day 0 as covariate

[redacted]

Table 51 Summary and Statistical Analysis of F_2 Pup Necropsy Weights on Postnatal Day 21 (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
MALES	79	86	85	74	77	74	70
Body Weight at Sacrifice (g)[a]							
	49 16 ΓΓΓ ± 0 77 ßßß N=79	47 97 ± 0 60 N=86	47 45 ± 1 03 N=85	45 71 ◊◊ ± 0 73 N=74	46 17 ◊◊ ± 0 79 N=77	47 69 ± 0 96 N=74	38 78 ◊◊◊ ± 1 02 N=70
Liver Weight (g)[a]							
	2 2947 ΓΓΓ ±0 0671 ßßß N=78[b]	2 2172 ±0 0395 N=86	2 1612 ±0 0654 N=85	2 0697 ◊ ±0 0496 N=74	2 0895 ◊ ±0 0564 N=77	2 2663 ±0 0649 N=74	1 7423 ◊◊◊ ±0 0527 N=70
Thymus Weight (g)[a]							
	0 2258 ΓΓΓ ±0 0047 ßßß N=79	0 2177 ±0 0055 N=86	0.2280 ±0 0070 N=85	0 2127 ±0 0050 N=74	0 2199 ±0 0069 N=77	0 2050 ◊◊ ±0.0053 N=73[b]	0 1950 ◊◊◊ ±0 0059 N=68[c]
Spleen Weight (g)[a]							
	0.2027 ΓΓΓ ±0 0048 ßßß N=78[c]	0 2082 ±0 0062 N=86	0 2004 ±0 0064 N=85	0 1911 ±0 0068 N=73[c]	0 1892 ±0 0077 N=77	0.1988 ±0 0063 N=73[b]	0 1388 ◊◊◊ ±0 0048 N=69[c]
Brain Weight (g)[a]							
	1 4540 ΓΓ ±0 0111 ßßß N=76[b,c]	1 4732 ±0 0104 N=85[c]	1 4603 ±0 0150 N=85	1 4470 ±0 0102 N=73[c]	1 4465 ±0 0122 N=77	1 4499 ±0 0134 N=74	1.4081 ◊◊ ±0 0124 N=70
Paired Testes Weight (g)[a]							
	0 2257 ΓΓΓ ±0 0043 ßßß N=79	0 2294 ±0 0053 N=86	0 2230 ±0 0064 N=85	0 2209 ±0 0050 N=74	0 2133 ±0 0058 N=77	0.2244 ±0 0061 N=74	0 1981 ◊◊◊ ±0 0054 N=70

(continued)

Table 51 Summary and Statistical Analysis of F_2 Pup Necropsy Weights on Postnatal Day 21 (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0.3	4 5	75	750	7500
Paired Epididymis Weight (g)[a]							
	0 0473 ±0 0022 N=79	0 0482 ±0 0017 N=85[c]	0 0494 ±0.0019 N=84[c]	0 0486 ±0 0018 N=74	0 0497 ±0 0017 N=77	0 0518 ±0 0026 N=73[b]	0 0528 ±0.0023 N=69[c]
Seminal Vesicles with Coagulating Gland Weight (g)[a]							
	0 0176 ±0 0010 N=76[c]	0 0201 ±0 0016 N=84[c,d]	0 0202 ±0 0020 N=82[c,d]	0 0197 ±0 0017 N=74	0 0197 ±0 0014 N=77	0 0231 ±0.0022 N=72[b,d]	0.0181 ±0 0014 N=69[c,d]
Relative Liver Weight (% of sacrifice weight)[a]							
	4 6555 ±0.0874 N=78[b]	4 6153 ±0 0498 N=86	4 5375 ±0 0681 N=85	4 5166 ±0 0591 N=74	4 5101 ±0.0707 N=77	4 7422 ±0 0823 N=74	4 4870 ±0.0501 N=70
Relative Thymus Weight (% of sacrifice weight)[a]							
	0 4600 ΓΓΓ ±0 0083 ßßß N=79	0 4540 ±0 0095 N=86	0 4797 ±0.0107 N=85	0 4648 ±0.0083 N=74	0 4779 ±0 0129 N=77	0 4323 ◊ ±0 0103 N=73[b]	0 5014 ◊◊◊ ±0 0078 N=68[c]
Relative Spleen Weight (% of sacrifice weight)[a]							
	0 4123 ΓΓΓ ±0 0067 ßßß N=78[c]	0 4326 ±0 0107 N=86	0 4205 ±0 0073 N=85	0 4166 ±0 0104 N=73[c]	0 4070 ±0 0121 N=77	0 4162 ±0 0089 N=73[b]	0 3578 ◊◊◊ ±0 0075 N=69[c]
Relative Brain Weight (% of sacrifice weight)[a]							
	2 9773 ΓΓΓ ±0 0406 ßßß N=76[b,c]	3 0951 ◊ ±0 0345 N=85[c]	3 1109 ◊ ±0 0483 N=85	3 1928 ◊◊ ±0.0513 N=73[c]	3 1649 ◊◊ ±0 0452 N=77	3 0721 ±0 0576 N=74	3 6929 ◊◊◊ ±0 0785 N=70

(continued)

Table 51 Summary and Statistical Analysis of F_2 Pup Necropsy Weights on Postnatal Day 21 (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Paired Testes Weight (% of sacrifice weight)[a]							
	0 4596 ΓΓΓ +0 0052 ßßß N=79	0 4777 +0 0077 N=86	0 4701 +0 0087 N=85	0 4838 ◊ +0 0095 N=74	0 4616 +0 0096 N=77	0 4702 +0 0074 N=74	0.5120 ◊◊◊ +0 0054 N=70
Relative Paired Epididymis Weight (% of sacrifice weight)[a]							
	0 0959 ΓΓΓ +0 0040 ßßß N=79	0 1009 +0 0031 N=85[c]	0 1050 +0 0142 N=84[c]	0 1067 +0 0037 N=74	0 1081 ◊ +0 0035 N=77	0 1089 ◊ +0 0048 N=73[b]	0 1388 ◊◊◊ +0.0074 N=69[c]
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight)[a]							
	0 0359 +0 0020 N=76[c]	0 0419 +0 0032 N=84[c,d]	0 0426 +0 0040 N=82[c,d]	0 0431 +0 0037 N=74	0 0431 +0.0031 N=77	0 0489 +0.0046 N=72[b,d]	0.0479 +0.0042 N=66[c,d]
FEMALES	77	90	79	72	80	77	59
Body Weight at Sacrifice (g)[a]							
	46 30 ΓΓΓ + 0 66 ßßß N=77	46 14 + 0 68 N=90	45.56 + 0 77 N=79	45 34 + 0 74 N=72	43 86 ◊ + 0 95 N=80	44.97 + 0 92 N=77	36 26 ◊◊◊ + 0 82 N=59
Liver Weight (g)[a]							
	2 2944 ΓΓΓ +0 0470 ßßß N=77	2.2559 +0.0450 N=90	2 2353 +0 0549 N=79	2 2388 +0 0548 N=72	2 0999 ◊ +0 0632 N=80	2 2023 +0 0572 N=77	1.6973 ◊◊◊ +0.0455 N=59
Thymus Weight (g)[a]							
	0 2221 ΓΓΓ +0.0058 ßßß N=76[b]	0.2210 +0.0063 N=88[e]	0 2290 +0 0066 N=78[b]	0 2277 +0 0072 N=72	0 2190 +0 0072 N=80	0 2112 +0 0068 N=75[b]	0 1942 ◊◊◊ +0 0040 N=59

(continued)

Table 51 Summary and Statistical Analysis of F_2 Pup Necropsy Weights on Postnatal Day 21 (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Spleen Weight (g)[a]							
	0 1993 ΓΓΓ ±0 0062 ßßß N=75[b,c]	0 2026 ±0 0064 N=90	0 1958 ±0 0068 N=78[b]	0 2011 ±0 0059 N=71[c]	0 1832 ◊ ±0 0062 N=80	0 1864 ±0 0080 N=75[b]	0 1340 ◊◊◊ ±0 0043 N=58[c]
Brain Weight (g)[a]							
	1 3950 ΓΓΓ ±0 0101 ßßß N=76[c]	1 4174 ±0 0110 N=89[c]	1 4034 ±0.0111 N=79	1 4124 ±0 0101 N=72	1 3856 ±0.0122 N=78[c]	1.4241 ◊ ±0 0099 N=77	1 3461 ◊◊ ±0.0107 N=59
Paired Ovary Weight (g)[a]							
	0 0312 Γ ±0 0014 ßßß N=76[b]	0 0332 ±0 0014 N=89[c]	0 0324 ±0 0016 N=78[b]	0 0337 ±0 0015 N=72	0 0326 ±0 0015 N=80[c]	0 0316 ±0 0017 N=75[b]	0 0271 ◊ ±0 0012 N=59
Uterus Weight (g)[a]							
	0 0955 ±0 0079 ßß N=76[b,c]	0 0832 ±0.0067 N=90	0 0812 ±0 0068 N=77[b,c]	0 0846 ±0 0061 N=72	0 0770 ±0 0053 N=80	0.0903 ±0.0074 N=75[b]	0 0667 ±0 0073 N=59
Relative Liver Weight (% of sacrifice weight)[a]							
	4.9491 Γ ±0.0704 ßß N=77	4 8831 ±0 0501 N=90	4 8787 ±0.0492 N=79	4 9204 ±0 0650 N=72	4 7766 ±0 0683 N=80	4 8930 ±0 0654 N=77	4 6769 ◊◊ ±0.0576 N=59
Relative Thymus Weight (% of sacrifice weight)[a]							
	0 4809 ΓΓΓ ±0 0095 ßßß N=76[b]	0 4798 ±0 0102 N=88[e]	0 5023 ±0 0104 N=78[b]	0 5013 ±0 0119 N=72	0 4981 ±0 0108 N=80	0 4685 ±0 0103 N=75[b]	0 5394 ◊◊◊ ±0 0123 N=59

(continued)

Table 51 Summary and Statistical Analysis of F_2 Pup Necropsy Weights on Postnatal Day 21 (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Spleen Weight (% of sacrifice weight)[a]							
	0 4306 ΓΓΓ ±0.0113 ßßß N=75[b,c]	0 4369 ±0 0101 N=90	0 4267 ±0 0097 N=78[b]	0 4415 ±0 0086 N=71[c]	0 4158 ±0 0098 N=80	0 4112 ±0 0122 N=75[b]	0 3696 ◊◊◊ ±0 0076 N=58[c]
Relative Brain Weight (% of sacrifice weight)[a]							
	3 0394 ΓΓΓ ±0 0408 ßßß N=76[c]	3 0976 ±0.0405 N=89[c]	3 1273 ±0 0574 N=79	3 1389 ±0 0416 N=72	3 2180 ◊ ±0 0553 N=78[c]	3 2002 ◊ ±0 0536 N=77	3 7544 ◊◊◊ ±0 0732 N=59
Relative Paired Ovary Weight (% of sacrifice weight)[a]							
	0.0674 ±0 0028 N=76[b]	0.0716 ±0 0027 N=89[c]	0 0709 ±0 0030 N=78[b]	0 0742 ±0 0028 N=72	0 0741 ±0 0027 N=80[c]	0 0700 ±0.0029 N=75[b]	0 0748 ±0.0029 N=59
Relative Uterus Weight (% of sacrifice weight)[a]							
	0.2068 ±0 0169 N=76[b,c]	0 1796 ±0 0141 N=90	0 1762 ±0 0136 N=77[b,c]	0 1876 ±0 0141 N=72	0 1748 ±0 0114 N=80	0 1985 ±0 0142 N=75[b]	0.1830 ±0 0188 N=59

[a]Reported as the mean ± S E M (adjusted for intralitter correlations)
[b]Decrease in N is due to one or more weights being unrealistic and therefore they were excluded
[c]Decrease in N is due to one or more weights being statistical outliers and therefore they were removed
[d]Decrease in N is due to one seminal vesicle weight inadvertently not being recorded
[e]Decrease in N is due to two thymus weights inadvertently not being recorded
Γp<0 05, Overall analysis of correlated data
ΓΓp<0 01, Overall analysis of correlated data
ΓΓΓp<0.001; Overall analysis of correlated data
ßßp<0 01, Test for Linear Trend on correlated data
ßßßp<0 001, Test for Linear Trend on correlated data
◊p<0 05, Pairwise comparison of correlated data.
◊◊p<0 01, Pairwise comparison of correlated data
◊◊◊p<0 001; Pairwise comparison of correlated data

Table 53 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes during the Post-Mating Holding Period (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 84) (g)[a]	519 5 ‡‡‡ ± 9 0 §§§ N=30	520 1 ± 7 9 N=30	519 3 ± 7 6 N=30	535 9 ± 6 9 N=29[b]	517 7 ± 7 2 N=30	485 8 * ± 8 3 N=30	386 1 *** ± 6 1 N=30
Body Weight (sd 91) (g)[a]	534 6 ‡‡‡ ± 9 8 §§§ N=30	535 7 ± 7 8 N=30	533 2 ± 8 2 N=30	550 2 ± 7 0 N=29	535 4 ± 7 5 N=30	502.3 * ± 8 8 N=30	399 3 *** ± 6.7 N=30
Body Weight (sd 98) (g)[a]	542 1 ‡‡‡ ± 9 3 §§§ N=30	542 5 ± 8 1 N=30	541 7 ± 8 2 N=30	562 7 ± 7.3 N=29	547 0 ± 7 4 N=30	511 5 * ± 8 8 N=30	404 4 *** ± 6 7 N=30
Body Weight (sd 105) (g)[a]	554 2 ‡‡‡ ± 9 5 §§§ N=29[c]	553 2 ± 9 3 N=30	553 6 ± 8.7 N=30	572 2 ± 7.7 N=29	555 3 ± 7.7 N=30	521.4 * ± 9.3 N=30	409 7 *** ± 7.4 N=30
Body Weight Change (sd 84 to 91) (g)[a]	15 0 ± 1 6 N=30	15 6 ± 1.8 N=30	13 9 ± 1 2 N=30	14 4 ± 1 1 N=29	17 7 ± 1 4 N=30	16 4 ± 1 4 N=30	13 2 ± 1 7 N=30
Body Weight Change (sd 91 to 98) (g)[a]	7 6 ‡ ± 1 5 § N=30	6 9 ± 1 9 N=30	8 5 ± 1.4 N=30	12 5 ± 1 5 N=29	11 6 ± 2 2 N=30	9 3 ± 1 6 N=30	5 1 ± 1 0 N=30

(continued)

Table 53 Summary and Statistical Analysis of the F_1 Male Body Weights and Weight Changes during the Post-Mating Holding Period (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 98 to 105) (g)[a]							
#	13 8 ¶¶ ± 1 2 ¥¥¥ N=29[c]	10 6 ± 2 0 N=30	11 9 ± 1 5 N=30	9 5 ¤ ± 1 5 N=29	8 3 ¤ ± 2 5 N=30	9 8 ¤ ± 1 1 N=30	5 3 ¤¤¤ ± 1 7 N=30

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the prebreed period
[b]Decrease in N is due to male 1315 being euthanized moribund on study day 72
[c]Decrease in N is due to male 1147 being found dead on study day 100
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶p<0 01, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 56 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Post-Mating Holding Period (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No Females on Study	30	30	30	30	30	30	29[a]
Body Weight (sd 84) (g)[b]	325 7 ± 9 2 N=2	335 6 ± 3 3 N=2	394 3 ± N=1	± N=0	320 9 ± N=1	271 1 ± N=1	228 0 ± . N=1
Body Weight (sd 91) (g)[b]	397.0 ± 6 5 N=2	380 2 ± 4 4 N=2	429 9 ± N=1	± N=0	305 6 ± N=1	275 1 ± N=1	271 7 ± N=1
Body Weight (sd 98) (g)[b]	312 3 ± 4 5 N=2	± N=0	± N=0	344.0 ± 27 4 N=4	338 5 ± 17 0 N=3	295 5 ± 13 2 N=4	211 8 ± 12 0 N=2
Body Weight (sd 105) (g)[b]	321 7 ± 3 8 N=2	± N=0	± N=0	346 3 ± 27 8 N=4	345 5 ± 14 3 N=3	301 8 ± 14 5 N=4	220 7 ± 4 9 N=2
Body Weight (sd 112) (g)[b]	326 2 ± 11 3 N=2	± N=0	± N=0	353 9 ± 30 6 N=4	350 1 ± 14 9 N=3	307 8 ± 14 3 N=4	232 2 ± 11 9 N=2

(continued)

Table 56 Summary and Statistical Analysis of the F_1 Female Body Weights and Weight Changes During the Post-Mating Holding Period (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4.500	75.000	750 000	7500 000
Body Weight Change (sd 84 to 91) (g)[b]							
	71.3 ± 2 7 N=2	44 5 ± 1 2 N=2	35 6 ± . N=1	± N=0	-15 3 ± N=1	4 0 ± N=1	43 7 ± N=1
Body Weight Change (sd 91 to 198) (g)[b]							
	± N=0	± N=0	± N=0	± N=0	2 2 ± N=1	8 0 ± N=1	± N=0
Body Weight Change (sd 98 to 105) (g)[b]							
	9 4 ± 0 6 N=2	± N=0	± N=0	2 3 ± 3 6 N=4	7 0 ± 2 8 N=3	6 4 ± 3 6 N=4	8 9 ± 7 1 N=2
Body Weight Change (sd 105 to 112) (g)[b]							
	4.6 ± 7 5 N=2	± . N=0	± N=0	7.6 ± 4 6 N=4	4 6 ± 0.6 N=3	6 0 ± 4 1 N=4	11 6 ± 7.0 N=2

[a]Animal 1214 was a male, not a female, as determined by histological examination of the reproductive tissues Therefore, no data is included for this animal

[b]Reported as the mean ± S E.M , sd=study day with study day 0 being the first day of the prebreed period Includes all females that were not found sperm and/or plug positive or females that did not have live litters or females whose entire litter died prior to postnatal day 21 Statistical analyses were not performed on these endpoints since not all females were represented

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 1 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
No Males at Terminal Sacrifice	29[a]	30	30	29[b]	30	30	30
Sacrifice Body Weight (g)[c]							
	566 00 ‡‡‡ ± 9 97 §§§ N=29	565 11 ± 9 40 N=30	566 04 ± 8 79 N=30	580 15 ± 9 30 N=29	566 56 ± 8 13 N=30	532 73 * ± 9 80 N=30	416 56 *** ± 7 64 N=30
Liver Weight (g)[c]							
	23 1694 ‡‡‡ ± 0 4689 §§§ N=29	23 5132 ± 0 5221 N=30	23 2891 ± 0.5177 N=30	24.3251 ± 0.4968 N=29	23 1147 ± 0 4863 N=30	21 0262 * ± 0 4752 N=30	16 4053 *** ± 0 3849 N=30
Paired Kidney Weight (g)[c]							
	4 5534 ‡‡‡ ± 0 0931 §§§ N=29	4 4466 ± 0.0694 N=29[d]	4 4386 ± 0 0816 N=30	4 4312 ± 0 0752 N=29	4 5349 ± 0 0635 N=30	4 2626 ± 0 1081 N=30	3 7044 *** ± 0 0638 N=30
Paired Adrenal Weight (g)[c]							
	0 0671 ± 0 0021 §§ N=29	0 0655 ± 0 0026 N=30	0 0643 ± 0 0027 N=29[d]	0 0673 ± 0 0019 N=29	0 0643 ± 0 0020 N=30	0 0676 ± 0 0027 N=30	0 0591 ± 0.0021 N=30
Spleen Weight (g)[c]							
	0 8807 ‡‡‡ ± 0 0231 §§§ N=29	0.8569 ± 0 0240 N=30	0 8692 ± 0 0192 N=30	0.9036 ± 0 0161 N=29	0 8325 ± 0 0261 N=30	0 8338 ± 0 0185 N=30	0.6972 *** ± 0 0144 N=29[d]
Brain Weight (g)[c]							
	2 1092 ‡‡‡ ± 0 0246 §§§ N=29	2 1261 ± 0 0196 N=30	2 1224 ± 0 0183 N=30	2 1331 ± 0 0207 N=29	2 1544 ± 0 0192 N=30	2 1191 ± 0 0170 N=30	1 9869 *** ± 0 0178 N=30

(continued)

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 2 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[c]							
	0 0169 ‡‡‡ ± 0 0003 §§§ N=29	0 0155 * ± 0 0004 N=29[e]	0 0165 ± 0 0004 N=28[e]	0 0164 ± 0 0003 N=28[e]	0 0176 ± 0.0004 N=29[e]	0 0154 * ± 0 0003 N=30	0 0146 *** ± 0 0004 N=29[e]
Paired Testes Weight (g)[c]							
	3 7170 ‡‡‡ ± 0 0540 §§§ N=28[d]	3 5703 ± 0 0660 N=30	3 5580 ± 0 0561 N=30	3 5595 ± 0 0905 N=29	3.5685 ± 0 0530 N=30	3.5555 ± 0.0618 N=30	3.2350 *** ± 0 0490 N=30
Paired Epididymis Weight (g)[c]							
	1 4455 ‡‡‡ ± 0 0215 §§§ N=28[d]	1 3826 ± 0 0173 N=30	1 4157 ± 0 0176 N=30	1 4368 ± 0 0201 N=29	1 4121 ± 0 0205 N=30	1 3908 ± 0 0218 N=30	1.2990 *** ± 0.0223 N=28[d,f]
Prostate Weight (g)[c]							
	0 7296 ‡‡ ± 0 0372 §§§ N=29	0.6967 ± 0 0288 N=30	0 7186 ± 0 0355 N=30	0.7804 ± 0 0426 N=29	0 7899 ± 0 0474 N=30	0 7647 ± 0.0418 N=30	0 5815 * ± 0.0248 N=30
Seminal Vesicles with Coagulating Glands Weight (g)[c]							
	2 1851 ‡‡‡ ± 0.0651 §§§ N=29	2 0951 ± 0 0638 N=30	2.1808 ± 0.0584 N=30	2 1954 ± 0.0529 N=29	2 2220 ± 0 0517 N=30	2.1322 ± 0 0599 N=30	1 8239 *** ± 0 0684 N=30
Preputial Gland Weight (g)[c]							
	0 2273 ‡ ± 0.0119 §§ N=28[g]	0 2199 ± 0 0152 N=30	0 1989 ± 0.0080 N=30	0 2365 ± 0.0140 N=29	0 2197 ± 0 0130 N=29[f]	0.2145 ± 0.0104 N=30	0 1773 * ± 0.0125 N=30

(continued)

[redacted]

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 3 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Liver Weight (% sacrifice weight)[c]							
	4 0951 ‡ ± 0 0456 §§ N=29	4 1546 ± 0 0455 N=30	4 1110 ± 0 0605 N=30	4 2099 ± 0 0926 N=29	4 0768 ± 0 0535 N=30	3 9465 ± 0 0513 N=30	3 9399 ± 0 0622 N=30
Relative Paired Kidney Weight (% sacrifice weight)[c]							
#	0 8056 ¶¶¶ ± 0 0115 ¥¥¥ N=29	0 7832 ± 0 0121 N=29[d]	0 7854 ± 0 0107 N=30	0 7665 ¤ ± 0 0129 N=29	0 8016 ± 0 0077 N=30	0 8043 ± 0 0199 N=30	0 8919 ¤¤¤ ± 0 0116 N=30
Relative Paired Adrenal Weight (% sacrifice weight)[c]							
	0 0120 ‡‡‡ ± 0 0004 §§§ N=29	0 0117 ± 0 0006 N=30	0 0115 ± 0 0005 N=29[d]	0 0117 ± 0 0004 N=29	0 0114 ± 0 0004 N=30	0 0128 ± 0 0005 N=30	0 0143 ** ± 0 0006 N=30
Relative Spleen Weight (% sacrifice weight)[c]							
#	0 1562 ¶¶¶ ± 0 0038 ¥ N=29	0 1522 ± 0 0044 N=30	0 1536 ± 0 0025 N=30	0 1564 ± 0 0030 N=29	0 1479 ¤ ± 0 0054 N=30	0.1571 ± 0 0032 N=30	0 1682 ¤¤ ± 0.0030 N=29[d]
Relative Brain Weight (% sacrifice weight)[c]							
	0 3755 ‡‡‡ ± 0 0071 §§§ N=29	0 3791 ± 0 0068 N=30	0 3774 ± 0 0062 N=30	0 3705 ± 0.0075 N=29	0 3825 ± 0 0064 N=30	0 4009 * ± 0 0065 N=30	0 4805 *** ± 0.0077 N=30
Relative Pituitary Weight (% sacrifice weight)[c]							
	0.0030 ‡‡‡ ± 0 0001 §§§ N=29	0 0028 ± 0 0001 N=29[e]	0 0029 ± 0 0001 N=28[e]	0 0028 ± 0 0001 N=28[e]	0 0031 ± 0 0001 N=29[e]	0 0029 ± 0 0001 N=30	0 0035 *** ± 0.0001 N=29[e]

(continued)

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 4 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Paired Testes Weight (% sacrifice weight)[c]							
	0 6627 ‡‡‡ ± 0 0137 §§§ N=28[d]	0 6355 ± 0 0136 N=30	0 6322 ± 0 0125 N=30	0 6183 ± 0 0198 N=29	0 6333 ± 0 0127 N=30	0 6709 ± 0 0119 N=30	0 7832 *** ± 0 0172 N=30
Relative Paired Epididymis Weight (% sacrifice weight)[c]							
	0 2569 ‡‡‡ ± 0.0051 §§§ N=28[d]	0 2462 ± 0 0043 N=30	0.2519 ± 0 0049 N=30	0 2493 ± 0.0053 N=29	0 2504 ± 0 0045 N=30	0 2627 ± 0 0048 N=30	0 3148 *** ± 0.0070 N=28[d,f]
Relative Prostate Weight (% sacrifice weight)[c]							
	0.1295 ± 0 0067 N=29	0 1234 ± 0 0046 N=30	0 1274 ± 0 0064 N=30	0 1358 ± 0.0078 N=29	0 1393 ± 0 0079 N=30	0 1427 ± 0 0066 N=30	0 1401 ± 0 0058 N=30
Relative Seminal Vesicles with Coagulating Glands Weight (% sacrifice weight)[c]							
	0 3875 ‡‡ ± 0 0109 §§§ N=29	0 3724 ± 0 0119 N=30	0 3869 ± 0 0107 N=30	0 3821 ± 0 0124 N=29	0 3940 ± 0 0099 N=30	0 4024 ± 0 0117 N=30	0 4387 * ± 0 0156 N=30
Relative Preputial Gland Weight (% sacrifice weight)[c]							
	0.0406 ± 0 0025 N=28[g]	0 0388 ± 0 0025 N=30	0 0352 ± 0 0013 N=30	0 0407 ± 0 0022 N=29	0 0389 ± 0 0024 N=29[f]	0 0405 ± 0.0020 N=30	0.0432 ± 0 0032 N=30
Percent Motile Sperm[c]							
	79 4 ± 1 0 N=29	78.6 ± 1 7 N=30	79 9 ± 1.4 N=30	79 0 ± 1 4 N=29	79 3 ± 1 5 N=30	81 0 ± 0 9 N=30	79 2 ± 1 2 N=30

(continued)

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at S
Evaluation (page 5 of 6)

	Bisphenol A (ppm in the feed)				
	0	0 015	0 3	4 5	75
Percent Progressively Motile Sperm[c]					
	66 5 ± 1 1 N=29	63 3 ± 1.8 N=30	64 7 ± 1 3 N=30	63 9 ± 1 3 N=29	64 9 ± 1 5 N=30
Epididymal Sperm Concentration (10^6/g)[c]					
	682 60 ‡ ± 33 25 §§§ N=29	645 25 ± 25 65 N=30	648 58 ± 28 48 N=30	653 18 ± 23 38 N=29	654 20 ± 20 86 N=30
Spermatid Head Concentration (10^6/g)[c]					
	114.84 ± 6 51 N=29	123 94 ± 6 73 N=30	111 47 ± 5 60 N=30	115 49 ± 6 44 N=29	114 20 ± 4 99 N=30
Daily Sperm Production per Testis (10^6/testis/day)[c]					
	46.19 ± 2 70 N=29	48 33 ± 2 55 N=30	42 78 ± 2 12 N=30	45 51 ± 2 80 N=29	44 42 ± 2 16 N=30
Efficiency of Daily Sperm Production (10^6/g. testis/day)[c]					
	24 91 ± 1 41 N=29	26 89 ± 1 46 N=30	24.18 ± 1 21 N=30	25 05 ± 1 40 N=29	24 77 ± 1 08 N=30
Percent Abnormal Sperm[c]					
#	1 98 ± 0 16 N=29	4 13 ± 2 20 N=30	3 44 ± 1.28 N=30	1 98 ± 0 15 N=29	2 41 ± 0 45 N=30

(continued)

Table 59 Summary and Statistical Analysis of the F_1 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 6 of 6)

---

[a]Male 1147 was found dead on study day 100
[b]Male 1315 was euthanized moribund on study day 72
[c]Reported as the mean ± S E M
[d]Decrease in N is due to one weight being a statistical outlier and therefore it was removed
[e]Decrease in N is due to the pituitary inadvertently not being saved for one or more males
[f]Decrease in N is due to the paired epididymis weight for one male inadvertently not being recorded
[g]Decrease in N is due to the preputial gland weight for one male inadvertently not being recorded
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥p<0 05, Jonckheere's Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 61 Summary and Statistical Analysis of the F_1 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
No Females at Scheduled Sacrifice	29[a]	30	30	30	30	30	28[b,c]
Sacrifice Body Weight (g)[d]							
	339 4 ‡‡‡ ± 5 6 §§§ N=29	347 0 ± 4.5 N=30	335 3 ± 4 3 N=30	340 4 ± 5 2 N=30	335 7 ± 4 7 N=30	318 2 * ± 5 0 N=30	283 7 *** ± 5 4 N=28
Liver Weight (g)[d]							
	18 5484 ‡‡ ± 0 5026 §§ N=28[e]	19 3961 ± 0 5233 N=30	18 8583 ± 0 4432 N=30	17 7038 ± 0 5895 N=30	17 4933 ± 0 4603 N=30	16 9622 ± 0 5141 N=30	16 6599 ± 0 5894 N=28
Paired Kidney Weight (g)[d]							
	2 9796 ‡‡‡ ± 0 0643 §§§ N=29	3 1076 ± 0 0382 N=30	3 0150 ± 0 0448 N=30	2 9385 ± 0 0518 N=30	2 9606 ± 0 0539 N=30	2 8610 ± 0 0537 N=30	2 5455 *** ± 0.0613 N=28
Paired Adrenal Weight (g)[d]							
	0 0950 ‡‡‡ ± 0 0038 §§§ N=29	0 1020 ± 0 0037 N=30	0 1007 ± 0 0032 N=29[f]	0 0963 ± 0.0034 N=30	0 0983 ± 0 0028 N=30	0.0967 ± 0 0031 N=30	0.0771 *** ± 0 0023 N=28
Spleen Weight (g)[d]							
	0 6094 ± 0 0159 N=29	0 6258 ± 0 0149 N=30	0 6212 ± 0 0153 N=30	0 6408 ± 0 0128 N=30	0 5836 ± 0 0155 N=30	0 5993 ± 0.0191 N=30	0 5816 ± 0 0188 N=28
Brain Weight (g)[d]							
	1 9418 ‡‡‡ ± 0 0213 §§§ N=28[g]	1 9476 ± 0 0140 N=30	1 9705 ± 0 0199 N=30	1 9478 ± 0 0211 N=30	1 9852 ± 0 0206 N=30	1 9302 ± 0 0238 N=30	1 7986 *** ± 0 0192 N=26[f]

(continued)

Table 61 Summary and Statistical Analysis of the F_1 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[d]							
	0 0192 ‡‡‡ ± 0 0006 §§§ N=26[h,i]	0 0201 ± 0 0005 N=29[f]	0 0186 ± 0 0006 N=25[h]	0 0185 ± 0 0005 N=28[h,i]	0 0197 ± 0 0007 N=30	0 0176 ± 0 0005 N=28[h]	0 0144 *** ± 0 0004 N=27[h]
Paired Ovary Weight (g)[d]							
	0 1800 ‡‡‡ ± 0 0061 §§§ N=29	0 1758 ± 0 0056 N=30	0 1778 ± 0 0050 N=30	0 1761 ± 0 0054 N=30	0 1760 ± 0 0055 N=30	0 1575 * ± 0 0059 N=30	0 1275 *** ± 0 0057 N=28
Uterus Weight (g)[d]							
	0 6581 ‡ ± 0 0350 §§§ N=29	0 6003 ± 0 0224 N=30	0 6341 ± 0 0282 N=30	0 6000 ± 0 0259 N=30	0 6076 ± 0 0230 N=30	0 6303 ± 0 0279 N=30	0 5141 ** ± 0 0229 N=28
Relative Liver Weight (% sacrifice weight)[d]							
	5.4646 ‡ ± 0 1301 §§ N=28[e]	5.5793 ± 0 1144 N=30	5 6298 ± 0 1226 N=30	5 2169 ± 0 1693 N=30	5 2122 ± 0 1196 N=30	5 3294 ± 0 1412 N=30	5 8503 ± 0 1647 N=28
Relative Paired Kidney Weight (% sacrifice weight)[d]							
	0 8785 ± 0 0138 N=29	0 8980 ± 0 0116 N=30	0 9011 ± 0.0128 N=30	0 8657 ± 0 0140 N=30	0.8840 ± 0 0154 N=30	0 9003 ± 0 0130 N=30	0 8970 ± 0 0137 N=28
Relative Paired Adrenal Weight (% sacrifice weight)[d]							
	0 0280 ± 0 0010 N=29	0 0294 ± 0 0010 N=30	0 0301 ± 0 0010 N=29[f]	0 0284 ± 0 0009 N=30	0 0295 ± 0.0010 N=30	0 0305 ± 0.0010 N=30	0 0272 ± 0.0007 N=28

(continued)

Table 61 Summary and Statistical Analysis of the F_1 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0.3	4 5	75	750	7500
Relative Spleen Weight (% sacrifice weight)[d]							
	0 1800 ‡‡‡ ± 0 0043 §§§ N=29	0 1806 ± 0 0040 N=30	0 1855 ± 0 0042 N=30	0 1893 ± 0 0044 N=30	0 1739 ± 0 0039 N=30	0 1881 ± 0.0047 N=30	0 2055 *** ± 0 0061 N=28
Relative Brain Weight (% sacrifice weight)[d]							
	0 5759 ‡‡‡ ± 0 0116 §§§ N=28[g]	0 5641 ± 0 0087 N=30	0 5898 ± 0 0080 N=30	0 5757 ± 0.0096 N=30	0 5935 ± 0 0077 N=30	0.6098 ± 0 0100 N=30	0 6406 ¤ ± 0.0157 N=26[f]
Relative Pituitary Weight (% sacrifice weight)[d]							
	0 0057 ‡ ± 0 0002 §§ N=26[h,i]	0 0058 ± 0.0001 N=29[f]	0 0056 ± 0.0002 N=25[h]	0 0055 ± 0 0001 N=28[h,i]	0 0059 ± 0 0002 N=30	0 0055 ± 0 0002 N=28[h]	0.0051 * ± 0.0001 N=27[h]
Relative Paired Ovary Weight (% sacrifice weight)[d]							
	0 0533 ‡ ± 0 0018 §§§ N=29	0 0508 ± 0 0017 N=30	0 0531 ± 0 0014 N=30	0 0519 ± 0 0016 N=30	0 0525 ± 0 0016 N=30	0 0493 ± 0 0014 N=30	0 0454 ** ± 0 0024 N=28
Relative Uterus Weight (% sacrifice weight)[d]							
	0 1953 ± 0 0116 N=29	0 1730 ± 0 0061 N=30	0 1896 ± 0 0082 N=30	0 1768 ± 0 0076 N=30	0 1825 ± 0 0077 N=30	0 1984 ± 0 0084 N=30	0 1826 ± 0 0088 N=28

(continued)

Table 61 Summary and Statistical Analysis of the F_1 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Paired Ovarian Follicle Count[d,j]							
	353 0 ± 35 4 N=10						409 7 ± 46 8 N=10
VAGINAL CYTOLOGY EVALUATION AT NECROPSY[k]							
No Females Evaluated	27[l]	30	29[l]	30	28[l]	30	28
No in Proestrus	5	8	3	3	5	4	4
% in Proestrus	20 00	26.67	10 34	10 34	18 52	14 29	15 38
No in Estrus	0	5	4	4	2	2	0
% in Estrus	0 00	16 67	13 79	13 79	7 41	7 14	0 00
No in Metestrus	2	0	2	0	0	0	0
% in Metestrus	8 00	0 00	6 90	0 00	0 00	0 00	0 00
No in Diestrus	18	17	20	22	20	22	22
% in Diestrus	72 00 Ψ	56.67	68 97	75 86	74 07	78 57	84 62
No Stage Not Determined	2	0	0	1	1	2	2
No No Cells Present	0	0	0	0	0	0	0

(continued)

Table 61 Summary and Statistical Analysis of the F_1 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 5)

---

[a]Female 1238 was found dead on lactational day 0 (study day 92) while in the process of delivering
[b]Animal 1214 was a male, not a female, as determined by histological examination of the reproductive tissues Therefore, no data is included for this animal
[c]Female 1204 was euthanized moribund on gestational day 15 (study day 87)
[d]Reported as the mean ± S E M
[e]Decrease in N is due to the liver weight for one female being unrealistic and therefore it was removed
[f]Decrease in N is due to one or more weights being statistical outliers and therefore they were removed
[g]Decrease in N is due to the brain weight for one female being unrealistic and therefore it was removed
[h]Decrease in N is due to the pituitary inadvertently not being saved for one or more females.
[i]Decrease in N is due to the pituitary being damaged or unidentifiable at the time of weighing for one female
[j]Ovarian follicle counts were done for 10 control females and 10 females in the 7500 000 ppm Bisphenol A dose group
[k]For 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, metestrus/estrus and estrus/diestrus 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
[l]Vaginal smear for one or more females inadvertently not done
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
Ψp<0 05; Cochran-Armitage Test

Table 64 Summary and Statistical Analysis of the F_2 Female Vaginal Opening and the F_2 Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0.015	0.300	4.500	75.000	750.000	7500.000
No of Females Evaluated	30	30	30	30	30	30	28[a]
Day of Vaginal Opening[b]							
#	31 0 ¶¶¶ ± 0 3 ¥¥¥ N=30	31.2 ± 0 4 N=30	31.2 ± 0.4 N=30	33 5 ± 2 2 N=30	32 1 ¤ ± 0 4 N=30	31 9 ± 0 4 N=30	34 5 ¤¤¤ ± 0 5 N=28
Body Weight (g) on Day of Acquisition[b]							
#	105 04 ± 1 97 N=30	106.47 ± 2 50 N=30	104 23 ± 2 29 N=30	114.63 ± 8 94 N=30	107 46 ± 2.06 N=30	105 14 ± 2.34 N=30	102 50 ± 2.89 N=28
Adjusted Day of Vaginal Opening[c]							
	31.3 δδδ ± 0.4 λλλ N=30	31.2 ± 0 4 N=30	31 7 ± 0.4 N=30	31 8 ± 0 4 N=30	31 9 ± 0 4 N=30	32.2 ± 0 4 N=30	35 3 φφφ ± 0 4 N=28
No of Males Evaluated	30	30	30	30	30	30	28[d]
Day of Preputial Separation[b]							
#	42.1 ¶¶¶ ± 0 3 ¥¥¥ N=30	43 5 ± 0.3 N=30	43 7 ¤¤ ± 0 4 N=30	42.9 ± 0.3 N=30	43 3 ¤¤ ± 0 3 N=30	43.2 ¤ ± 0 3 N=30	47.9 ¤¤¤ ± 1 8 N=28
Body Weight (g) on Day of Acquisition[b]							
	219.74 ‡‡‡ ± 3.76 §§§ N=30	228.70 ± 3 34 N=30	223.26 ± 3 97 N=30	217.31 ± 3.20 N=30	219.83 ± 2.93 N=30	211.36 ± 3.63 N=30	200 13 ** ± 5.28 N=28

(continued)

[redacted]

Table 64 Summary and Statistical Analysis of the F_2 Female Vaginal Opening and the F_2 Male Preputial Separation Data (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4.500	75 000	750.000	7500 000
Adjusted Day of Preputial Separation[c]							
	41 9 δδδ ± 0.6 λλλ N=30	41 6 ± 0 7 N=30	43 2 ± 0 6 N=30	42 9 ± 0.6 N=30	43 1 ± 0.6 N=30	43 8 ± 0 6 N=30	49 3 φφφ ± 0.7 N=28

[a]Female 2058 was found dead on study day -7 and female 2354 was found dead on study day -8 during the holding period after weaning and prior to the start of the prebreed period

[b]Reported as the mean ± S.E.M with day being postnatal day.

[c]Reported as the adjusted mean (body weight as covariate) ± S.E M , pnd=postnatal day.

[d]Male 2265 was found dead on study day -8 and male 2377 were found dead on study day -9 during the holding period after weaning and prior to the start of the prebreed period.

#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

¶¶¶p<0 001, Kruskal-Wallis Test.

¥¥¥p<0 001, Jonckheere's Test

¤p<0 05; Mann-Whitney U Test.

¤¤p<0 01; Mann-Whitney U Test

¤¤¤p<0 001, Mann-Whitney U Test

δδδp<0 001, Analysis of Covariance with body weight on day of acquisition as covariate .

λλλp<0 001; Linear Trend Analysis of Covariance with body weight on day of acquisition as covariate

φφφp<0 001, Dunnett's Test with body weight on day of acquisition as covariate.

‡‡‡p<0 001; ANOVA Test.

§§§p<0 001, Test for Linear Trend

**p<0 01, Dunnett's Test.

[redacted]

Table 65 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]							
	118.8 ‡‡‡ ± 3 5 §§§ N=30	118 9 ± 2 7 N=30	117 4 ± 3 4 N=30	114 0 ± 4 4 N=30	113 3 ± 3 5 N=30	113 6 ± 3 1 N=30	98 1 *** ± 2.7 N=28[b]
Body Weight (sd 7) (g)[a]							
	179 9 ‡‡‡ ± 3 9 §§§ N=30	182 3 ± 3 4 N=30	176 8 ± 4 3 N=30	173 8 ± 5 3 N=30	173 4 ± 4 5 N=30	171 0 ± 3.8 N=30	147.1 *** ± 3 2 N=28
Body Weight (sd 14) (g)[a]							
	245 1 ‡‡‡ ± 4 7 §§§ N=30	247.9 ± 3 6 N=30	238 4 ± 5 1 N=30	235 3 ± 5 9 N=30	233 1 ± 4 8 N=30	226 5 * ± 4 4 N=30	192 4 *** ± 3 9 N=28
Body Weight (sd 21) (g)[a]							
	304 7 ‡‡‡ ± 5 3 §§§ N=30	303 3 ± 4 2 N=30	296 5 ± 5 9 N=30	290 2 ± 6 3 N=30	285 6 ± 5 1 N=30	275 3 *** ± 5 3 N=30	229.7 *** ± 4.5 N=28
Body Weight (sd 28) (g)[a]							
	361 8 ‡‡‡ ± 6 0 §§§ N=30	361 8 ± 4 2 N=30	352 7 ± 6 1 N=30	347 1 ± 6 9 N=30	344 9 ± 5 5 N=30	325 1 *** ± 5.7 N=30	270 7 *** ± 5 2 N=28
Body Weight (sd 35) (g)[a]							
	401 0 ‡‡‡ ± 6 6 §§§ N=30	405 5 ± 4 6 N=30	392 4 ± 7.1 N=30	387 9 ± 7 2 N=30	385 8 ± 5 6 N=30	359 6 *** ± 6 1 N=30	294 2 *** ± 5 6 N=28

(continued)

Table 65 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 42) (g)[a]							
	439.6 ‡‡‡ ± 7.1 §§§ N=30	445 2 ± 5 1 N=30	428 2 ± 7 6 N=30	425 3 ± 7 7 N=30	422 6 ± 6 1 N=30	391 7 *** ± 6 3 N=30	317 8 *** ± 6 0 N=28
Body Weight (sd 49) (g)[a]							
	465 7 ‡‡‡ ± 7 6 §§§ N=30	472 0 ± 5 8 N=30	452 0 ± 8 4 N=30	450 7 ± 7 8 N=30	447 9 ± 6 5 N=30	416 0 *** ± 6 4 N=30	332 4 *** ± 6.8 N=28
Body Weight (sd 56) (g)[a]							
	483.2 ‡‡‡ ± 8 0 §§§ N=30	494 9 ± 6 6 N=30	467 6 ± 7 8 N=30	468.6 ± 8 0 N=30	466 1 ± 6 8 N=30	431 8 *** ± 6 2 N=30	345.2 *** ± 6 7 N=28
Body Weight (sd 63) (g)[a]							
	503 8 ‡‡‡ ± 8.5 §§§ N=30	512 6 ± 6 4 N=30	487 1 ± 8 7 N=30	487 6 ± 8 3 N=30	484 4 ± 7 1 N=30	443 4 *** ± 7 4 N=30	355 6 *** ± 6 6 N=28
Body Weight (sd 70) (g)[a]							
	521 0 ‡‡‡ ± 8 8 §§§ N=30	529 6 ± 7 4 N=30	503 5 ± 9 4 N=30	504 0 ± 8 8 N=30	501 7 ± 7 6 N=30	463 3 *** ± 7 1 N=29[c]	371.0 *** ± 6 8 N=28
Body Weight (sd 77) (g)[a]							
	521 5 ‡‡‡ ± 7 9 §§§ N=30	535 6 ± 7 7 N=30	509 0 ± 9 4 N=30	512 3 ± 8 8 N=30	506 7 ± 7 1 N=30	468 8 *** ± 6 8 N=29	375 5 *** ± 7 2 N=28

(continued)

Table 65 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 84) (g)[a]							
	545 1 ‡‡‡	554.5	525.6	528 6	522 3	483 8 ***	390 2 ***
	± 8 5 §§§	± 8 0	± 9 4	± 9 0	± 7 7	± 6 6	± 7 2
	N=30	N=30	N=30	N=30	N=30	N=29	N=28
Body Weight Change (sd 0 to 7) (g)[a]							
	61 1 ‡‡‡	63 3	59 4	59 8	60 1	57 4	48 9 ***
	± 1 6 §§§	± 1 1	± 1 3	± 1 2	± 1 1	± 1 0	± 1 1
	N=30	N=30	N=30	N=30	N=30	N=30	N=28[b]
Body Weight Change (sd 7 to 14) (g)[a]							
	65.1 ‡‡‡	65 6	61 7	61 5	59 7 *	55 5 ***	45 3 ***
	± 1 7 §§§	± 0 9	± 1 2	± 1 2	± 1 2	± 1 4	± 1 6
	N=30	N=30	N=30	N=30	N=30	N=30	N=28
Body Weight Change (sd 14 to 21) (g)[a]							
	59 6 ‡‡‡	55 4	58 1	54 8	52 5 **	48 8 ***	37 3 ***
	± 1 3 §§§	± 1 9	± 1 4	± 1 2	± 1 7	± 1 4	± 1 2
	N=30	N=30	N=30	N=30	N=30	N=30	N=28
Body Weight Change (sd 21 to 28) (g)[a]							
	57 0 ‡‡‡	58 5	56 1	57 0	59 3	49 8 *	41.0 ***
	± 1 7 §§§	± 1 5	± 1.4	± 1 8	± 2 1	± 1 1	± 1.6
	N=30	N=30	N=30	N=30	N=30	N=30	N=28
Body Weight Change (sd 28 to 35) (g)[a]							
	39 2 ‡‡‡	43 7	39 7	40 8	40 9	34 5	23 6 ***
	± 1 3 §§§	± 2 0	± 1 5	± 1.2	± 1 2	± 1 5	± 1.5
	N=30	N=30	N=30	N=30	N=30	N=30	N=28

(continued)

Table 65 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 35 to 42) (g)[a]							
	38 7 ‡‡‡ ± 1 2 §§§ N=30	39 7 ± 1 0 N=30	35 8 ± 0 9 N=30	37 4 ± 1 1 N=30	36 8 ± 1 2 N=30	32 1 *** ± 1 2 N=30	23.6 *** ± 1 3 N=28
Body Weight Change (sd 42 to 49) (g)[a]							
	26 1 ‡‡‡ ± 1 3 §§§ N=30	26 8 ± 1 2 N=30	23 8 ± 1 5 N=30	25 4 ± 1 2 N=30	25 3 ± 1 6 N=30	24.3 ± 1 3 N=30	14.6 *** ± 2.1 N=28
Body Weight Change (sd 49 to 56) (g)[a]							
#	17 5 ¶¶ ± 1 2 ¥¥¥ N=30	22 9 ± 3 4 N=30	15 5 ± 1.5 N=30	18 0 ± 1 2 N=30	18 1 ± 1 3 N=30	15 7 ± 1 0 N=30	12 8 ¤¤ ± 1.2 N=28
Body Weight Change (sd 56 to 63) (g)[a]							
#	20 6 ¶¶¶ ± 0.9 ¥¥¥ N=30	17.7 ± 3.5 N=30	19 5 ± 1 3 N=30	19 0 ± 1 1 N=30	18 3 ± 1 0 N=30	11 7 ¤¤¤ ± 3 3 N=30	10 4 ¤¤¤ ± 1 0 N=28
Body Weight Change (sd 63 to 70) (g)[a]							
	17 1 ± 0 9 N=30	17.0 ± 1 5 N=30	16 5 ± 1 3 N=30	16 4 ± 1 0 N=30	17 3 ± 0 9 N=30	16 5 ± 0 8 N=29[c]	15 4 ± 1 3 N=28
Body Weight Change (sd 0 to 70) (g)[a]							
	402.1 ‡‡‡ ± 7 6 §§§ N=30	410 6 ± 6 8 N=30	386 1 ± 7.8 N=30	390 0 ± 7 1 N=30	388 4 ± 6 3 N=30	349 5 *** ± 5 3 N=29	272 9 *** ± 6.6 N=28

(continued)

Table 65 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Prebreed and Mating Periods (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 70 to 77) (g)[a]							
#	0 5 ± 3 2 N=30	6 0 ± 2 2 N=30	5 4 ± 1 4 N=30	8 3 ± 1 3 N=30	5 0 ± 1 3 N=30	5 5 ± 1 2 N=29	4 5 ± 1 6 N=28
Body Weight Change (sd 77 to 84) (g)[a]							
#	23 6 ¶¶ ± 2 2 ¥¥¥ N=30	19 0 ± 1 2 N=30	16 6 ¤ ± 1 1 N=30	16 3 ¤¤ ± 1 0 N=30	15 7 ¤¤ ± 1 3 N=30	14.9 ¤¤¤ ± 1 2 N=29	14 7 ¤¤ ± 1 7 N=28

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the prebreed period

[b]Decrease in N is due to male 2265 being found dead on study day -8 and male 2377 being found dead on study day -9 (negative study days were during the holding period after weaning and prior to the start of the prebreed period).

[c]Decrease in N is due to male 2365 being euthanized moribund on study day 63

#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed

‡‡‡p<0 001, ANOVA Test

§§§p<0 001, Test for Linear Trend

*p<0 05, Dunnett's Test

**p<0 01, Dunnett's Test

***p<0 001, Dunnett's Test

¶¶p<0.01, Kruskal-Wallis Test

¶¶¶p<0 001, Kruskal-Wallis Test

¥¥¥p<0 001, Jonckheere's Test

¤p<0.05, Mann-Whitney U Test

¤¤p<0.01, Mann-Whitney U Test

¤¤¤p<0 001, Mann-Whitney U Test.

Table 68. Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500 000
No Females on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]							
	104 8 ‡‡‡ ± 2 3 §§§ N=30	102 5 ± 2.5 N=30	106 0 ± 3 0 N=30	102 7 ± 3 2 N=30	100 6 ± 3 2 N=30	100.9 ± 2 2 N=30	85 6 *** ± 2 0 N=28[b]
Body Weight (sd 7) (g)[a]							
	147.8 ‡‡‡ ± 2 4 §§§ N=30	144.4 ± 2 6 N=30	141 1 ± 3 6 N=30	143 1 ± 3 2 N=30	142.6 ± 3.4 N=30	140 2 ± 2.6 N=30	120 7 *** ± 2.2 N=28
Body Weight (sd 14) (g)[a]							
	177 4 ‡‡‡ ± 2 6 §§§ N=30	175.6 ± 2.9 N=30	172 4 ± 3 4 N=30	174 2 ± 3 0 N=30	174 2 ± 3 7 N=30	169 7 ± 3 3 N=30	148 3 *** ± 1.9 N=28
Body Weight (sd 21) (g)[a]							
	202.0 ‡‡‡ ± 3 2 §§§ N=30	198 6 ± 3.1 N=30	195.3 ± 3.8 N=30	201.0 ± 3 9 N=30	198.3 ± 4 0 N=30	191 6 ± 3 8 N=30	164 7 *** ± 1 8 N=28
Body Weight (sd 28) (g)[a]							
	225.7 ‡‡‡ ± 3.7 §§§ N=30	223.2 ± 3.7 N=30	219 2 ± 4.5 N=30	225 6 ± 4.0 N=30	223.0 ± 4.4 N=30	213.8 ± 4 4 N=30	180.8 *** ± 2 4 N=28
Body Weight (sd 35) (g)[a]							
#	241.0 ¶¶¶ ± 3 8 ¥¥¥ N=30	239.6 ± 4.2 N=30	234 0 ± 5 0 N=30	240 2 ± 4 4 N=30	239 2 ± 4.6 N=30	229.3 ¤ ± 4 8 N=30	191 3 ¤¤¤ ± 2 1 N=28

(continued)

Table 68 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During the Prebreed and Mating Periods
(page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4.500	75 000	750 000	7500.000
Body Weight (sd 42) (g)[a]							
	254 1 ‡‡‡ ± 3 9 §§§ N=30	255 3 ± 4 3 N=30	246 6 ± 5.5 N=30	256 5 ± 4.7 N=30	253 5 ± 4 9 N=30	241 8 ± 5.3 N=29[c]	198.7 *** ± 2 3 N=28
Body Weight (sd 49) (g)[a]							
	266 5 ‡‡‡ ± 4.5 §§§ N=30	268 6 ± 5 0 N=30	260.9 ± 5.6 N=30	269.6 ± 5.0 N=30	266.1 ± 4.8 N=30	253 5 ± 5.7 N=30	207 4 *** ± 2 6 N=28
Body Weight (sd 56) (g)[a]							
	275 9 ‡‡‡ ± 4 7 §§§ N=30	276 6 ± 4 7 N=30	270 2 ± 5 9 N=30	280 2 ± 5 3 N=30	275 7 ± 5 2 N=30	264 6 ± 6.0 N=30	213 4 *** ± 2 8 N=28
Body Weight (sd 63) (g)[a]							
	287 7 ‡‡‡ ± 5 3 §§§ N=30	291 3 ± 5 3 N=30	284 6 ± 6 5 N=30	291 8 ± 5.7 N=30	284 6 ± 5 6 N=30	276 9 ± 6 7 N=30	221 2 *** ± 3 3 N=28
Body Weight (sd 70) (g)[a]							
	290.3 ‡‡‡ ± 5 3 §§§ N=30	294 2 ± 5 2 N=30	286 7 ± 6.2 N=30	293 6 ± 5 7 N=30	287 7 ± 5 6 N=30	278 4 ± 6.6 N=30	225 6 *** ± 3 5 N=28
Body Weight (sd 77) (g)[a,d]							
	262 8 ± 6.4 N=3	299 4 ± 1 8 N=2	285 6 ± N=1	304 6 ± 28 5 N=3	339 5 ± N=1	336 4 ± . N=1	± . N=0

(continued)

Table 68 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 3 of 5)

		Bisphenol A (ppm in the feed)						
		0 000	0 015	0 300	4.500	75 000	750.000	7500 000
Body Weight (sd 84) (g)[a,d]								
		313.6 ± 13 6 N=2	331 6 ± 5 1 N=2	± N=0	316 5 ± 39 5 N=2	355.4 ± N=1	356 9 ± N=1	± N=0
Body Weight Change (sd 0 to 7) (g)[a]								
	#	43 1 ¶¶¶ ± 1 3 ¥¥¥ N=30	41 9 ± 0 9 N=30	35 1 ¤ ± 3 4 N=30	40 4 ± 1 2 N=30	42 0 ± 1 0 N=30	39 3 ± 0 9 N=30	35 1 ¤¤¤ ± 0 8 N=28[b]
Body Weight Change (sd 7 to 14) (g)[a]								
	#	29 6 ± 1 0 N=30	31 1 ± 1 3 N=30	31 3 ± 2 4 N=30	31 0 ± 1 5 N=30	31 5 ± 0 9 N=30	29.5 ± 1.1 N=30	27 6 ± 0.9 N=28
Body Weight Change (sd 14 to 21) (g)[a]								
	#	24.6 ¶¶¶ ± 1.3 ¥¥¥ N=30	23 1 ± 0.9 N=30	22 9 ± 1.4 N=30	26 8 ± 1 7 N=30	24 1 ± 1 1 N=30	21 9 ± 1 0 N=30	16 3 ¤¤¤ ± 0 8 N=28
Body Weight Change (sd 21 to 28) (g)[a]								
		23 8 ‡‡‡ ± 1.3 §§§ N=30	24 5 ± 1 2 N=30	23 9 ± 1 2 N=30	24 6 ± 1 1 N=30	24 8 ± 1 0 N=30	22 2 ± 1 2 N=30	16 1 *** ± 1 0 N=28
Body Weight Change (sd 28 to 35) (g)[a]								
		15.2 ‡ ± 1.3 §§§ N=30	16.5 ± 1.3 N=30	14.7 ± 1.3 N=30	14.6 ± 1 0 N=30	16 2 ± 1 2 N=30	15 5 ± 1 1 N=30	10 5 * ± 1 0 N=28

(continued)

Table 68 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75.000	750 000	7500 000
Body Weight Change (sd 35 to 42) (g)[a]							
	13 1 ‡‡‡ ± 1 1 §§§ N=30	15 6 ± 1.0 N=30	12 7 ± 1 0 N=30	16 4 ± 1 1 N=30	14 3 ± 1 2 N=30	12.3 ± 1 0 N=29[c]	7.4 ** ± 1 0 N=28
Body Weight Change (sd 42 to 49) (g)[a]							
	12 4 ‡ ± 1 3 §§§ N=30	13 3 ± 1.4 N=30	14 2 ± 1 0 N=30	13 0 ± 1 0 N=30	12 6 ± 1 0 N=30	11 8 ± 1 1 N=29[c]	8 7 ± 0 8 N=28
Body Weight Change (sd 49 to 56) (g)[a]							
	9 4 ± 1 5 § N=30	8 0 ± 1 4 N=30	9 4 ± 1 1 N=30	10 6 ± 1 3 N=30	9.6 ± 1 5 N=30	11 1 ± 1 1 N=30	6.0 ± 1 1 N=28
Body Weight Change (sd 56 to 63) (g)[a]							
	11.8 ‡ ± 2 0 § N=30	14 7 ± 2 0 N=30	14 4 ± 1 8 N=30	11 6 ± 1.5 N=30	8 9 ± 1 4 N=30	12.3 ± 1 4 N=30	7 9 ± 1 2 N=28
Body Weight Change (sd 63 to 70) (g)[a]							
	2 6 ± 1 5 N=30	2 9 ± 1.3 N=30	2 0 ± 1 5 N=30	1 8 ± 1 6 N=30	3 2 ± 1 5 N=30	1 5 ± 1 2 N=30	4 4 ± 0 8 N=28
Body Weight Change (sd 0 to 70) (g)[a]							
	185 5 ‡‡‡ ± 5 7 §§§ N=30	191 7 ± 4 7 N=30	180 7 ± 4 7 N=30	190 9 ± 5.5 N=30	187 1 ± 5 3 N=30	177.5 ± 5 4 N=30	140.1 *** ± 3 4 N=28

(continued)

Table 68 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During the Prebreed and Mating Periods (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Body Weight Change (sd 70 to 77) (g)[a,d]							
	-16 2 ± 6 2 N=3	-7 1 ± 0 4 N=2	10 5 ± N=1	-0 8 ± 7 3 N=3	4 3 ± N=1	-10.7 ± N=1	± N=0
Body Weight Change (sd 77 to 84) (g)[a,d]							
	46 6 ± 21 9 N=2	32.2 ± 6.9 N=2	± N=0	7 6 ± 9.3 N=2	15 9 ± N=1	20 5 ± N=1	± N=0

[a]Reported as the mean ± S E M ; sd=study day with study day 0 being the first day of the prebreed period
[b]Decrease in N is due to female 2058 being found dead on study day -7 and female 2354 being found dead on study day -8 (negative study days were during the holding period after weaning and prior to the start of the prebreed period)
[c]Decrease in N is due to the body weight for one female being a statistical outlier and it was therefore removed
[d]Includes all females that were not found sperm and/or plug positive Statistical analyses were not performed on these endpoints since not all females were represented
‡p<0 05, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§§p<0 001; Test for Linear Trend
*p<0.05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0.001; Kruskal-Wallis Test
¥¥¥p<0 001; Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01; Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 72 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During Gestation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0,300	4 500	75,000	750 000	7500 000
No. Sperm Positive Pregnant Females	27	28	29	26	28	27	27
Body Weight (gd 0) (g)[a]	285.4 ‡‡‡ ± 5 2 §§§ N=27	287 0 ± 5 3 N=28	282 1 ± 5 8 N=29	283 4 ± 4 7 N=26	283 2 ± 5 3 N=28	271 6 ± 6 4 N=27	221 0 *** ± 3 5 N=27
Body Weight (gd 7) (g)[a]	312 0 ‡‡‡ ± 5 4 §§§ N=27	315 1 ± 5 0 N=28	305 0 ± 5 9 N=29	309 8 ± 5 1 N=26	306 8 ± 5 5 N=28	293 1 ± 6 5 N=27	241 8 *** ± 3 5 N=27
Body Weight (gd 14) (g)[a]	339 9 ‡‡‡ ± 5 7 §§§ N=27	342 0 ± 5 2 N=28	332 2 ± 6.4 N=29	336 2 ± 5 4 N=26	333 7 ± 5 4 N=28	320 2 ± 7 3 N=27	263 4 *** ± 3 4 N=27
Body Weight (gd 20) (g)[a]	414 3 ‡‡‡ ± 7 0 §§§ N=27	416 1 ± 5 9 N=28	398 4 ± 7.1 N=29	399.4 ± 5.1 N=24[b]	403 9 ± 6 2 N=28	391 0 ± 8 6 N=27	320 0 *** ± 4 6 N=27
Body Weight Change (gd 0 to 7) (g)[a]	26.7 ‡‡‡ ± 0.9 §§ N=27	28.1 ± 1 2 N=28	22 9 ± 1 4 N=29	26 4 ± 1.4 N=26	23 6 ± 1 5 N=28	21.5 * ± 1 9 N=27	20 7 * ± 1 2 N=27

(continued)

Table 72 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During Gestation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75.000	750 000	7500 000
Body Weight Change (gd 7 to 14) (g)[a]							
	27 8 ‡	26 9	27 2	26 4	26.9	27 1	21 6 **
	± 1 1 §§§	± 1 0	± 0 8	± 1 7	± 1.6	± 1 6	± 1 0
	N=27	N=28	N=29	N=26	N=28	N=27	N=27
Body Weight Change (gd 14 to 20) (g)[a]							
	74 4 ‡‡‡	74 1	66 2 *	66 1	70 2	70.8	56.6 ***
	± 1 9 §§§	± 1 8	± 2 1	± 3 2	± 2 4	± 2.1	± 2 1
	N=27	N=28	N=29	N=24[b]	N=28	N=27	N=27
Body Weight Change (gd 0 to 20) (g)[a]							
	128 9 ‡‡‡	129 0	116 3 *	117 4 *	120 7	119 5	99 0 ***
	± 2 9 §§§	± 2.7	± 2 9	± 3 2	± 2 9	± 3 3	± 3 1
	N=27	N=28	N=29	N=24[b]	N=28	N=27	N=27

[a]Reported as the mean ± S E M , gd=gestational day.

[b]Decrease in N is due to female 2044 being in the process of delivering at the time of weighing on gestatonal day 20 and therefore the body weight was not taken and female 2268 had delivered on gestational day 17

‡p<0 05, ANOVA Test.

‡‡‡p<0 001, ANOVA Test

§§p<0 01, Test for Linear Trend

§§§p<0.001, Test for Linear Trend

*p<0 05, Dunnett's Test

***p<0 001, Dunnett's Test

Table 75. Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During Lactation (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500.000
No Females with Litters on Postnatal Day 0	28	29	29	26[a]	28	27[b]	27
Body Weight (pnd 0) (g)[c]	319 4 ‡‡‡ ± 5 9 §§§ N=28	324.0 ± 4 9 N=29	313 6 ± 6 7 N=29	307 0 ± 4 0 N=25	314 9 ± 5 4 N=28	298.2 * ± 7 1 N=26	247 2 *** ± 3 9 N=27
Body Weight (pnd 4) (g)[c]	332 3 ‡‡‡ ± 5.9 §§§ N=28	335.2 ± 4 5 N=29	321 8 ± 4 9 N=28[d]	321 3 ± 3 7 N=25	326.4 ± 5 0 N=28	315.9 ± 7 1 N=26	253.3 *** ± 3.7 N=27
Body Weight (pnd 7) (g)[c]	342 5 ‡‡‡ ± 6 0 §§§ N=28	345 7 ± 4.4 N=29	329 7 ± 4 6 N=28	329 8 ± 3 5 N=25	337 3 ± 4 8 N=28	328 3 ± 7 0 N=26	267 3 *** ± 3 9 N=27
Body Weight (pnd 14) (g)[c]	355 8 ‡‡‡ ± 5 7 §§§ N=28	356.3 ± 4 0 N=29	340 0 ± 4 8 N=28	342 4 ± 3.8 N=25	344.9 ± 5.1 N=28	342 1 ± 6 7 N=26	287 0 *** ± 4.5 N=27
Body Weight (pnd 21) (g)[c]	328 8 ‡‡‡ ± 4 6 §§§ N=28	340 8 ± 3 6 N=29	321.5 ± 3 7 N=28	317 7 ± 3 5 N=25	324 8 ± 4 9 N=28	324 8 ± 6 1 N=26	283 9 *** ± 3.8 N=27

(continued)

Table 75 Summary and Statistical Analysis of the F_2 Female Body Weights and Weight Changes During Lactation (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4.500	75.000	750 000	7500 000
Body Weight Change (pnd 0 to 4) (g)[c]							
	12.9	11 2	12.3	14 3	11 5	17 7	6 1
	± 2.3 §	± 1 8	± 2 3	± 2 3	± 2 5	± 3 4	± 2 4
	N=28	N=29	N=28[d]	N=25	N=28	N=26	N=27
Body Weight Change (pnd 4 to 7) (g)[c]							
	10 2	10 5	7.9	8 5	10.9	12.5	14.0
	± 1 8 §	± 1 6	± 1 3	± 1 6	± 1 4	± 1 6	± 1.4
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Body Weight Change (pnd 7 to 14) (g)[c]							
	13 3 ‡	10.6	10.3	12 5	7 6	13.7	19 7
	± 2 5 §§§	± 2.2	± 1 5	± 3 3	± 2 5	± 2 3	± 1 6
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Body Weight Change (pnd 14 to 21) (g)[c]							
	-27.0 ‡‡‡	-15.5 *	-18 5	-24 7	-20 1	-17 2	-3 1 ***
	± 3.2 §§§	± 2 0	± 2.8	± 3 1	± 3 4	± 3 0	± 2.9
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Body Weight Change (pnd 0 to 21) (g)[c]							
	9 4 ‡‡‡	16 8	12 0	10 6	10 0	26 6 **	36 6 ***
	± 3.6 §§§	± 2.7	± 3 4	± 3.8	± 3.5	± 4 1	± 3.0
	N=28	N=29	N=28	N=25	N=28	N=26	N=27

[a]Female 2178 was pregnant but did not deliver a litter (had implant sites only).
[b]Female 2062 had a live litter but here postnatal day 0 date was inadvertently not recorded
[c]Reported as the mean ± S E M ; pnd=postnatal day.
[d]Decrease in N is due to the entire litter of female 2284 being dead or euthanized moribund on or before postnatal day 3
‡p<0 05, ANOVA Test ‡‡‡p<0 001; ANOVA Test.
§p<0 05, Test for Linear Trend §§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test **p<0 01, Dunnett's Test ***p<0.001, Dunnett's Test

Table 78. Summary and Statistical Analysis of the F_2 Reproductive and Lactational Indexes for the F_3 Litters (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0.015	0.300	4.500	75.000	750.000	7500.000
No. Animals on Study							
Males	30	30	30	30	30	30	30
Females	30	30	30	30	30	30	30
No. Females Paired							
	30	30	30	30	30	30	28[a]
No. Females that Mated							
	29	29	30	28	29	29	28
Mating Index (no. females that mated/no. females paired)							
	96.7	96.7	100.0	93.3	96.7	96.7	100.0
No. of Pregnant Females							
	28	29	29	26	28	27	27
Fertility Index (no. pregnant females/no. females that mated)							
	96.6	100.0	96.7	92.9	96.6	93.1	96.4
No. of Females with Live Litters (pnd 0)							
	28	29	29	25[b]	28	27	27
Gestational Index (no. females with live litters/no. females pregnant)							
	100.0	100.0	100.0	96.2	100.0	100.0	100.0

(continued)

Table 78 Summary and Statistical Analysis of the F_2 Reproductive and Lactational Indexes for the F_3 Litters (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75.000	750 000	7500 000
No Males Paired							
	30	30	30	30	30	29[c]	27[d]
No Males that Mated							
	29	29	30	28	29	28	27
Mating Index (no males that mated/no. males paired)							
	96 7	96 7	100 0	93 3	96 7	96 6	100 0
No Males Siring Litters							
	28	29	29	25	28	27	26
Fertility Index (no males siring litters/no males that mated)							
	96 6	100 0	96 7	89 3	96 6	96 4	96 3
Pregnancy Index (no pregnant females/no. males that mated)							
	96 6	100 0	96 7	92.9	96.6	96 4	100 00
Days until Sperm Positive (days)[e,f]							
#	3 1 + 0 4 N=28	2 0 + 0.2 N=28	2.8 + 0 5 N=30	2.7 + 0 3 N=28	2 9 + 0.3 N=29	2 7 + 0.2 N=29	3 1 + 0 3 N=28
Gestational Length (days)[e,g]							
#	22 0 + 0 1 N=27	22 3 + 0 1 N=28	22 0 + 0 1 N=29	22 0 + 0 3 N=25	22 1 + 0 1 N=28	22.0 + 0 1 N=26	22 1 + 0 1 N=27

(continued)

Table 78 Summary and Statistical Analysis of the F_2 Reproductive and Lactational Indexes for the F_3 Litters (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4.500	75 000	750.000	7500 000
No of Live Litters							
Postnatal Day 0	28	29	29	25	28	27[h]	27
Postnatal Day 4	28	29	28[i]	25	28	27	27
Postnatal Day 7	28	29	28	25	28	27	27
Postnatal Day 14	28	29	28	25	28	27	27
Postnatal Day 21	28	29	28	25	28	27	27
No Implantation Sites per Litter[e]							
#	15.25 ¶¶¶ + 0 33 ¥¥¥ N=28	15 03 + 0 38 N=29	14 03 ¤ + 0 53 N=29	14.19 + 0 73 N=26	15 11 + 0 39 N=28	14 44 + 0 33 N=27	12.44 ¤¤¤ + 0 29 N=27
Percent Postimplantation Loss per Litter[e]	5 02 + 1 14 § N=28	7 17 + 1.60 N=29	6.59 + 1.57 N=29	10 88 + 3 92 N=26	9 26 + 1.77 N=28	6 87 + 1 35 N=26[h]	12 30 + 2 17 N=27
Number of Live Pups on Postnatal Day 0[e]	14 8 ‡‡‡ + 0.4 §§§ N=28	14 1 + 0 4 N=29	13 2 * + 0 5 N=29	13 6 + 0 6 N=25	13 9 + 0.4 N=28	13 7 + 0 4 N=26	10.9 *** + 0 4 N=27
Number of Dead Pups on Postnatal Day 0[e]	0 1 + 0.1 N=28	0 2 + 0.1 N=29	0 1 + 0 0 N=29	0.2 + 0 1 N=25	0 2 + 0 1 N=28	0 2 + 0 1 N=26	0 3 + 0.1 N=27
Total Number of Pups on Postnatal Day 0[e]	14 9 ‡‡‡ + 0.4 §§§ N=28	14.3 + 0 4 N=29	13 3 * + 0 5 N=29	13 8 + 0 6 N=25	14 1 + 0.4 N=28	13 8 + 0 4 N=26	11 2 *** + 0 4 N=27

(continued)

Table 78. Summary and Statistical Analysis of the F_2 Reproductive and Lactational Indexes for the F_3 Litters (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500 000
Stillbirth Index (no. dead on pnd 0/total no on pnd 0)[e]							
	0 7 + 0 4 § N=28	1 2 + 0 7 N=29	0 5 + 0.3 N=29	1 1 + 0 6 N=25	1 2 + 0 5 N=28	1.1 + 0 6 N=26	2 6 + 0 9 N=27
Live Birth Index (no live on pnd 0/total no on pnd 0)[e]							
	99.3 + 0.4 § N=28	98.8 + 0 7 N=29	99.5 + 0.3 N=29	98 9 + 0 6 N=25	98 8 + 0 5 N=28	98 9 + 0 6 N=26	97 4 + 0 9 N=27
4 Day Survival Index (no surviving 4 days/no live on pnd 0)[e]							
#	96.1 + 1 4 N=28	98.0 + 1 0 N=29	94 5 + 3 4 N=29	98.3 + 0 6 N=25	98 4 + 0 8 N=28	97 6 + 0 9 N=26	99 1 + 0 5 N=27
7 Day Survival Index (no surviving 7 days/no live on pnd 4)[e]							
#	99 3 + 0.5 N=28	99 7 + 0 3 N=29	99 6 + 0 4 N=28	100.0 + 0 0 N=25	99.6 + 0 4 N=28	100 0 + 0 0 N=26	99 6 + 0 4 N=27
14 Day Survival Index (no surviving 14 days/no live on pnd 7)[e]							
#	100.0 + 0 0 N=28	99 3 + 0 5 N=29	99 2 + 0 5 N=28	100 0 + 0 0 N=25	98 9 + 0 6 N=28	99 6 + 0 4 N=26	99 3 + 0 7 N=27
21 Day Survival Index (no surviving 21 days/no. live on pnd 14)[e]							
#	100 0 + 0 0 N=28	99 7 + 0.3 N=29	100.0 + 0 0 N=28	100 0 + 0 0 N=25	100 0 + 0 0 N=28	100 0 + 0 0 N=26	100.0 + 0.0 N=27

(continued)

Table 78 Summary and Statistical Analysis of the F_2 Reproductive and Lactational Indexes for the F_3 Litters (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750 000	7500 000
Lactational Index (no surviving 21 days/no live on pnd 4)[e]							
#	99 3 + 0.5 N=28	98 6 + 0 8 N=29	98 9 + 0.8 N=28	100 0 + 0 0 N=25	98 6 + 0 8 N=28	99 6 + 0 4 N=26	98 8 + 0 8 N=27

[a]Female 2058 was found dead on study day -7 and female 2354 was found dead on study day -8 (study day 0 was the first day of the prebreed period)
[b]Female 2178 had implant sites only.
[c]Male 2365 was euthanized moribund on study day 63 (study day 0 was the first day of the prebreed period)
[d]Male 2265 was found dead on study day -8 and male 2377 was found dead on study day -9 (study day 0 was the first day of the prebreed period) Male 2069 in cohort 1 was not mated because there were only 29 females available Since both males that died were from cohort 2 and there were 29 females in cohort 2, one male in cohort 2 was mated with two females, therefore a total of only 27 males were mated.
[e]Reported as the mean ± S.E M , pnd=postnatal day All indexes are the average percent per litter
[f]*Days until sperm positive could only be calculated for those females for which sperm were detected in the vaginal smear*
[g]Gestational length could not be calculated for females that were pregnant, but for which sperm were never detected in the vaginal smear.
[h]Female 2062 had a live litter but here postnatal day 0 date was inadvertently not recorded She was included as a pregnant female with a live litter and her number of implants was included, but no other reproductive or lactational indexes were included since it was unkown how many live and dead pups she had on postnatal day 0.
[i]The entire litter for female 2284 was dead, missing and presumed dead or euthanized moribund on or before postnatal day 3
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
¶¶¶p<0 001, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test.
¤¤¤*p<0 001, Mann-Whitney U Test*
‡‡‡p<0 001; ANOVA Test.
§p<0 05, Test for Linear Trend
§§§p<0 001, Test for Linear Trend.
*p<0 05, Dunnett's Test
***p<0 001, Dunnett's Test.

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 1 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4.500	75.000	750 000	7500 000
No of Live Litters							
Postnatal Day 0	28	29	29	25	28	27[a]	27
Postnatal Day 4	28	29	28[b]	25	28	27	27
Postnatal Day 7	28	29	28	25	28	27	27
Postnatal Day 14	28	29	28	25	28	27	27
Postnatal Day 21	28	29	28	25	28	27	27
Average Number of Pups per Litter (pnd 0)[c]							
	14.8 ‡‡‡	14 1	13.2 *	13 6	13 9	13 7	10 9 ***
	± 0 4 §§§	± 0.4	± 0 5	± 0 6	± 0 4	± 0.4	± 0.4
	N=28	N=29	N=29	N=25	N=28	N=26	N=27
Average Number of Pups per Litter (pnd 4)[c]							
	14 2 ‡‡‡	13.8	12 4	13 4	13 7	13.3	10.8 ***
	± 0 4 §§§	± 0.4	± 0 7	± 0 6	± 0 4	± 0 4	± 0 4
	N=28	N=29	N=29	N=25	N=28	N=26	N=27
Average Number of Pups per Litter (pnd 7)[c]							
#	9 9	9 9	9 6	9.7	9 8	10 0	9.5
	± 0.0	± 0 0	± 0 3	± 0 3	± 0 1	± 0.0	± 0 2
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Average Number of Pups per Litter (pnd 14)[c]							
#	9 9	9.9	9 5	9 7	9 7	9.9	9 4
	± 0 0	± 0.1	± 0 3	± 0.3	± 0 1	± 0 1	± 0 2
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Average Number of Pups per Litter (pnd 21)[c]							
#	9.9	9 8	9 5	9 7	9 7	9.9	9 4
	± 0 0	± 0 1	± 0 3	± 0 3	± 0 1	± 0 1	± 0 2
	N=28	N=29	N=28	N=25	N=28	N=26	N=27

(continued)

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 2 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Average **Male** Anogenital Distance (mm) per Litter (pnd 0)[c]							
#	1 97	1 97	1 97	2 00	2 01	2 00	1.96
	± 0 02	± 0 02	± 0 04	± 0 03	± 0.02	± 0 02	± 0.02
	N=28	N=29	N=29	N=25	N=28	N=26	N=27
Average Adjusted **Male** Anogenital Distance (mm) per Litter (pnd 0)[d]							
	1 98	1 95	1 97	1 99	2 02	2.00	1 96
	± 0 02	± 0 02	± 0 02	± 0 03	± 0 02	± 0 03	± 0 02
	N=28	N=29	N=29	N=25	N=28	N=26	N=27
Average **Female** Anogenital Distance (mm) per Litter (pnd 0)[c]							
	0 92	0 96	0 91	0 93	0 95	0 95	0 94
	± 0 02	± 0.02	± 0 02	± 0 02	± 0 01	± 0 01	± 0.01
	N=28	N=29	N=29	N=25	N=28	N=26	N=27
Average Adjusted **Female** Anogenital Distance (mm) per Litter (pnd 0)[d]							
	0 93	0 95	0 91	0 92	0 96	0 95	0 94
	± 0 02	± 0 01	± 0 01	± 0 02	± 0 02	± 0 02	± 0 02
	N=28	N=29	N=29	N=25	N=28	N=26	N=27

(continued)

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 3 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Average Pup Body Weight (g) per Litter (pnd 0)[c]							
	6 16 ± 0 09 N=28	6 51 ± 0 10 N=29	6 32 ± 0 08 N=29	6 46 ± 0 15 N=25	6 21 ± 0 10 N=28	6 31 ± 0 12 N=26	6 32 ± 0 08 N=27
Average **Male** Body Weight (g) per Litter (pnd 0)[c]							
	6 36 ± 0 10 N=28	6 71 ± 0 10 N=29	6.51 ± 0 08 N=29	6.66 ± 0 15 N=25	6.40 ± 0 10 N=28	6.49 ± 0.12 N=26	6 49 ± 0 08 N=27
Average **Female** Body Weight (g) per Litter (pnd 0)[c]							
	5.98 ± 0 09 N=28	6 34 ± 0 10 N=29	6 14 ± 0 08 N=29	6 31 ± 0 15 N=25	5 99 ± 0 09 N=28	6 10 ± 0 13 N=26	6 14 ± 0 07 N=27
Average Pup Body Weight (g) per Litter (pnd 4)[c]							
	9 60 ± 0 29 N=28	10 12 ± 0 25 N=29	9 96 ± 0.17 N=28	10 28 ± 0 40 N=25	10 04 ± 0 24 N=28	9 87 ± 0 26 N=26	9 46 ± 0 23 N=27
Average **Male** Body Weight (g) per Litter (pnd 4)[c]							
	9 92 ± 0 30 § N=28	10 37 ± 0 25 N=29	10 27 ± 0 18 N=28	10 45 ± 0 42 N=25	10 25 ± 0.27 N=28	10 08 ± 0.26 N=26	9 63 ± 0.24 N=27
Average **Female** Body Weight (g) per Litter (pnd 4)[c]							
	9 28 ± 0 28 N=28	9 91 ± 0 25 N=29	9 66 ± 0 17 N=28	10 14 ± 0 40 N=25	9 78 ± 0 22 N=28	9 54 ± 0 28 N=26	9.31 ± 0 22 N=27

(continued)

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 4 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750 000	7500 000
Average Pup Body Weight (g) per Litter (pnd 7)[c]							
	15 41 ‡‡‡	15 72	15.73	16 37	15 89	15 31	13 42 **
	± 0 42 §§§	± 0 37	± 0 23	± 0 53	± 0.41	± 0 41	± 0 38
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Average **Male** Body Weight (g) per Litter (pnd 7)[c]							
	15 92 ‡‡‡	16 07	16.20	16 73	16 19	15 72	13.88 **
	± 0 44 §§§	± 0 37	± 0 23	± 0 56	± 0 44	± 0 41	± 0 35
	N=28	N=29	N=28	N=25	N=28	N=26	N=26[e]
Average **Female** Body Weight (g) per Litter (pnd 7)[c]							
	14 88 ‡‡‡	15 35	15 26	16 06	15 59	14 83	13 11 *
	± 0 42 §§§	± 0 38	± 0 26	± 0 53	± 0 40	± 0 44	± 0.39
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Average Pup Body Weight (g) per Litter (pnd 14)[c]							
	32 15 ‡‡‡	32 28	31 74	32 59	32.55	31 33	25.72 ***
	± 0 53 §§§	± 0 52	± 0 40	± 0 65	± 0 56	± 0 62	± 0 64
	N=28	N=29	N=28	N=25	N=28	N=26	N=27
Average **Male** Body Weight (g) per Litter (pnd 14)[c]							
	33 03 ‡‡‡	32 84	32 57	33.24	33 00	31 99	26 60 ***
	± 0 55 §§§	± 0 58	± 0 46	± 0 70	± 0 60	± 0 60	± 0 55
	N=28	N=29	N=28	N=25	N=28	N=26	N=26[e]
Average **Female** Body Weight (g) per Litter (pnd 14)[c]							
	31 26 ‡‡‡	31.70	30 93	32.01	32 12	30 54	25.13 ***
	± 0 53 §§§	± 0 50	± 0 41	± 0 65	± 0 55	± 0 72	± 0.68
	N=28	N=29	N=28	N=25	N=28	N=26	N=27

(continued)

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 5 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Average Pup Body Weight (g) per Litter (pnd 21)[c]							
	46 66 ‡‡‡ ± 0 67 §§§ N=28	46 70 ± 0.74 N=29	46 29 ± 0 59 N=28	47 50 ± 1 28 N=25	47 18 ± 0 67 N=28	44 76 ± 0 77 N=26	37 97 *** ± 0.89 N=27
Average **Male** Body Weight (g) per Litter (pnd 21)[c]							
	48.12 ‡‡‡ ± 0 75 §§§ N=28	48 11 ± 0 81 N=29	47 80 ± 0 69 N=28	48 78 ± 1 39 N=25	47 93 ± 0 75 N=28	45 89 ± 0 81 N=26	39 17 *** ± 0 83 N=26[e]
Average **Female** Body Weight (g) per Litter (pnd 21)[c]							
	45 18 ‡‡‡ ± 0 68 §§§ N=28	45 34 ± 0 74 N=29	44 86 ± 0.61 N=28	46 39 ± 1 27 N=25	46 48 ± 0 65 N=28	43 53 ± 0 84 N=26	37 01 *** ± 0 94 N=27
Percent Male Pups per Litter (pnd 0)[c]							
	45 2 ± 2 6 N=28	44 9 ± 2 9 N=29	47 4 ± 1 7 N=29	44 6 ± 2 2 N=25	51.4 ± 2 2 N=28	54 1 ± 2 5 N=26	48 7 ± 3 6 N=27
Percent Male Pups per Litter (pnd 4)[c]							
	44 8 ± 2 7 N=28	46 4 ± 2 8 N=29	47 2 ± 1 9 N=28	45 9 ± 2 2 N=25	51 5 ± 2 2 N=28	54 4 ± 2 7 N=26	49 0 ± 3 6 N=27
Percent Male Pups per Litter (pnd 7)[c]							
#	46 3 ± 2 1 N=28	49 5 ± 2 0 N=29	49 5 ± 1 1 N=28	48 1 ± 1 3 N=25	50 1 ± 0 8 N=28	52.5 ± 1 6 N=26	49 6 ± 3 5 N=27

(continued)

TX

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 6 of 7)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Percent Male Pups per Litter (pnd 14)[c]							
#	46 3 ± 2 1 N=28	49 5 ± 2 0 N=29	49 9 ± 1 1 N=28	48 1 ± 1 3 N=25	49 8 ± 0 9 N=28	52.3 ± 1 6 N=26	49 6 ± 3 5 N=27
Percent Male Pups per Litter (pnd 21)[c]							
#	46 3 ± 2 1 N=28	49 3 ± 2 0 N=29	49 9 ± 1 1 N=28	48 1 ± 1 3 N=25	49 8 ± 0 9 N=28	52 3 ± 1 6 N=26	49.6 ± 3 5 N=27
No of Nipples per Animal[f]							
	0 00 ± 0 00 N=129	0 00 ± 0 00 N=142	0 00 ± 0 00 N=134	0 00 ± 0 00 N=118	0 00 ± 0 00 N=137	0.00 ± 0 00 N=139	0 00 ± 0.00 N=127
Percent with One or More Nipples							
	0 00	0 00	0 00	0 00	0 00	0 00	0 00
No of Areolae per Animal[f]							
	0 00 ± 0 00 ß N=129	0.03 ± 0.02 N=142	0 01 ± 0 01 N=134	0 00 ± 0 00 N=118	0 06 ± 0 03 N=137	0 03 ± 0 02 N=139	0 00 ± 0 00 N=127
Percent with One or More Areolae							
	0.00	1 41	0 75	0 00	2 92	1 44	0 00

(continued)

Table 79 Summary and Statistical Analysis of the F_3 Litter Size, F_3 Pup Anogenital Distance, F_3 Pup Body Weights, Percent F_3 Males and F_3 Male Nipple Evaluations During Lactation (page 7 of 7)

[a]Female 2062 had a live litter but here postnatal day 0 date was inadvertently not recorded

[b]The entire litter for female 2284 was dead, missing and presumed dead or euthanized moribund on or before postnatal day 3

[c]Reported as the mean ± S.E.M., pnd=postnatal day

[d]Reported as the adjusted mean (body weight as covariate) ± S.E.M., pnd=postnatal day

[e]Decrease in N is due to one female having a litter of all female pups.

[f]Reported as the mean ± S.E.M. (adjusted for intralitter correlations)

[#]Bartlett's test for homogeneity of variances was significant ($p<0.001$) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed

[‡‡‡]$p<0.001$, ANOVA Test

[§]$p<0.05$; Test for Linear Trend

[§§§]$p<0.001$, Test for Linear Trend

[*]$p<0.05$, Dunnett's Test.

[**]$p<0.01$, Dunnett's Test

[***]$p<0.001$, Dunnett's Test

[ß]$p<0.05$, Test for Linear Trend on correlated data

Table 82 Summary and Statistical Analysis of F_3 Pup Necropsy Weights on Postnatal Day 21 (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
MALES	76	84	81	70	83	81	69
Body Weight at Sacrifice (g)[a]							
	48.65 ΓΓΓ ± 0.78 ßßß N=76	47 36 ± 0.81 N=84	46 95 ± 0 64 N=81	47 38 ± 0 99 N=70	47 33 ± 0 72 N=83	45 25 ◊◊ ± 0 85 N=81	38 58 ◊◊◊ ± 0.83 N=69
Liver Weight (g)[a]							
	2.1883 ΓΓΓ ±0 0470 ßßß N=76	2 2419 ±0.0680 N=84	2.1029 ±0 0442 N=81	2 1296 ±0 0622 N=70	2.1511 ±0.0480 N=83	1.9579 ◊◊◊ ±0 0455 N=81	1 6932 ◊◊◊ ±0.0491 N=69
Thymus Weight (g)[a]							
	0.2198 ΓΓΓ ±0 0068 ßß N=76	0 2094 ±0.0060 N=84	0 2189 ±0.0044 N=81	0 2182 ±0 0058 N=70	0 2173 ±0.0053 N=83	0 1947 ◊◊ ±0.0051 N=81	0.1938 ◊◊ ±0 0070 N=69
Spleen Weight (g)[a]							
	0 2074 ΓΓΓ ±0.0074 ßßß N=75[b]	0 2043 ±0 0074 N=84	0 1961 ±0.0060 N=81	0 2131 ±0 0084 N=70	0 1965 ±0 0065 N=83	0 1845 ◊ ±0 0046 N=81	0 1443 ◊◊◊ ±0 0057 N=69
Brain Weight (g)[a]							
	1 4654 Γ ±0.0120 ßßß N=76	1.4627 ±0 0111 N=84	1 4732 ±0 0084 N=81	1 4604 ±0.0100 N=70	1.4622 ±0.0117 N=82[b]	1 4500 ±0.0154 N=81	1.4112 ◊◊ ±0 0147 N=69
Paired Testes Weight (g)[a]							
	0 2354 ΓΓΓ ±0 0062 ßßß N=76	0.2303 ±0 0060 N=84	0 2264 ±0.0043 N=81	0 2374 ±0 0061 N=68[c]	0.2275 ±0 0055 N=83	0 2250 ±0 0053 N=81	0 2024 ◊◊◊ ±0 0051 N=69

(continued)

Table 82 Summary and Statistical Analysis of F_3 Pup Necropsy Weights on Postnatal Day 21 (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Paired Epididymis Weight (g)[a]							
	0 0575 ±0 0016 N=75[b]	0.0566 ±0.0018 N=84	0.0560 ±0.0014 N=80[b]	0 0575 ±0 0013 N=70	0 0580 ±0 0015 N=82[b]	0 0586 ±0 0018 N=80[c]	0 0552 ±0 0018 N=69
Seminal Vesicles with Coagulating Gland Weight (g)[a]							
	0 0219 ±0 0017 ßß N=75[b]	0.0209 ±0 0014 N=80[b,d]	0 0191 ±0.0012 N=76[b,d]	0 0192 ±0.0009 N=67[b]	0 0199 ±0 0009 N=81[d]	0 0213 ±0 0019 N=79[b,d]	0 0176 ±0 0009 N=67[b]
Relative Liver Weight (% of sacrifice weight)[a]							
	4 4842 Γ ±0 0421 ß N=76	4.7154 ◊ ±0 1100 N=84	4 4654 ±0 0590 N=81	4 4794 ±0 0721 N=70	4.5386 ±0.0614 N=83	4 3216 ◊ ±0 0524 N=81	4 3801 ±0 0624 N=69
Relative Thymus Weight (% of sacrifice weight)[a]							
	0.4512 ΓΓΓ ±0 0111 ßßß N=76	0 4431 ±0 0094 N=84	0 4676 ±0 0081 N=81	0 4621 ±0 0104 N=70	0 4588 ±0.0090 N=83	0.4322 ±0.0107 N=81	0 4991 ◊◊ ±0 0109 N=69
Relative Spleen Weight (% of sacrifice weight)[a]							
	0.4257 ΓΓΓ ±0.0106 ßßß N=75[b]	0 4281 ±0 0108 N=84	0 4160 ±0.0092 N=81	0.4464 ±0 0116 N=70	0 4132 ±0 0102 N=83	0 4078 ±0.0085 N=81	0 3714 ◊◊◊ ±0 0093 N=69
Relative Brain Weight (% of sacrifice weight)[a]							
	3 0364 ΓΓΓ ±0 0466 ßßß N=76	3 1280 ±0 0463 N=84	3 1606 ±0 0363 N=81	3 1209 ±0.0645 N=70	3 1102 ±0 0410 N=82[b]	3 2331 ◊◊ ±0 0436 N=81	3 6973 ◊◊◊ ±0 0690 N=69

(continued)

Table 82 Summary and Statistical Analysis of F_3 Pup Necropsy Weights on Postnatal Day 21 (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4.5	75	750	7500
Relative Paired Testes Weight (% of sacrifice weight)[a]							
	0.4832 ΓΓΓ ±0 0079 ßßß N=76	0 4861 ±0 0085 N=84	0 4834 ±0 0077 N=81	0 5010 ±0 0079 N=68[c]	0 4804 ±0 0081 N=83	0 4979 ±0 0083 N=81	0 5244 ◊◊◊ ±0 0064 N=69
Relative Paired Epididymis Weight (% of sacrifice weight)[a]							
	0.1184 ΓΓΓ ±0 0029 ßßß N=75[b]	0 1196 ±0 0033 N=84	0 1197 ±0 0027 N=80[b]	0 1219 ±0 0025 N=70	0 1224 ±0.0023 N=82[b]	0 1297 ◊ ±0 0033 N=80[c]	0 1438 ◊◊◊ ±0 0041 N=69
Relative Seminal Vesicles with Coagulating Gland Weight (% of sacrifice weight)[a]							
	0 0457 ±0 0038 N=75[b]	0.0446 ±0 0030 N=80[b,d]	0.0412 ±0.0028 N=76[b,d]	0.0408 ±0.0021 N=67[b]	0 0423 ±0.0020 N=81[d]	0.0472 ±0 0042 N=79[b,d]	0 0459 ±0.0024 N=67[b]
FEMALES	84	83	80	73	83	77	69
Body Weight at Sacrifice (g)[a]							
	44 32 ΓΓΓ ± 0 81 ßßß N=84	44 76 ± 0 71 N=83	44.03 ± 0 65 N=80	45 08 ± 0 92 N=73	45 67 ± 0 72 N=83	42.26 ± 0 93 N=77	36 15 ◊◊◊ ± 0 91 N=69
Liver Weight (g)[a]							
	2.0752 ΓΓΓ ±0 0460 ßßß N=84	2 2123 ±0 0630 N=83	2 0562 ±0 0433 N=80	2.0758 ±0 0594 N=72[b]	2.1843 ±0 0420 N=83	1 9352 ◊ ±0.0524 N=77	1.6444 ◊◊◊ ±0.0598 N=69
Thymus Weight (g)[a]							
	0 2139 ΓΓΓ ±0 0069 ßß N=84	0 2179 ±0 0060 N=83	0 2220 ±0 0052 N=80	0 2168 ±0 0067 N=73	0 2218 ±0 0053 N=83	0 1952 ◊ ±0 0058 N=77	0 1937 ◊ ±0 0069 N=69

(continued)

Table 82 Summary and Statistical Analysis of F_3 Pup Necropsy Weights on Postnatal Day 21 (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Spleen Weight (g)[a]							
	0 1886 ΓΓΓ +0 0063 ßßß N=84	0 1956 +0 0062 N=83	0 1863 +0 0049 N=80	0 2020 +0 0069 N=73	0 1968 +0 0062 N=83	0 1743 +0 0054 N=77	0 1383 ◊◊◊ +0.0055 N=69
Brain Weight (g)[a]							
	1.4042 ΓΓ +0 0112 ßßß N=84	1 4204 +0 0089 N=82[c]	1 4216 +0 0089 N=80	1 4107 +0 0097 N=71[b,c]	1 4012 +0 0116 N=83	1 4069 +0.0154 N=76[e]	1 3485 ◊◊ +0 0148 N=69
Paired Ovary Weight (g)[a]							
	0 0347 Γ +0 0011 ßßß N=84	0 0347 +0 0013 N=82[f]	0 0351 +0 0011 N=80	0 0347 +0 0009 N=73	0 0369 +0 0012 N=83	0 0346 +0 0014 N=77	0.0301 ◊ +0 0014 N=69
Uterus Weight (g)[a]							
	0 0771 ΓΓ +0 0045 ßßß N=84	0 0703 +0 0041 N=83	0.0799 +0.0038 N=80	0.0764 +0 0041 N=73	0 0811 +0 0037 N=83	0 0804 +0 0048 N=77	0.0624 ◊ +0 0040 N=68[g]
Relative Liver Weight (% of sacrifice weight)[a]							
	4 6766 ΓΓ +0 0378 ßß N=84	4 9423 ◊ +0 1089 N=83	4 6618 +0 0559 N=80	4 6203 +0 0554 N=72[b]	4 7781 +0 0467 N=83	4 5695 +0 0566 N=77	4 5151 +0 0734 N=69
Relative Thymus Weight (% of sacrifice weight)[a]							
	0.4825 ΓΓΓ +0 0118 ßßß N=84	0.4867 +0.0100 N=83	0 5043 +0 0097 N=80	0 4822 +0 0116 N=73	0.4858 +0 0104 N=83	0.4617 +0 0094 N=77	0.5325 ◊◊ +0 0118 N=69

(continued)

Table 82 Summary and Statistical Analysis of F_3 Pup Necropsy Weights on Postnatal Day 21 (page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Spleen Weight (% of sacrifice weight)[a]							
	0 4233 ΓΓΓ ±0 0091 ßßß N=84	0 4354 ±0 0100 N=83	0 4222 ±0 0084 N=80	0.4452 ±0.0101 N=73	0 4290 ±0 0094 N=83	0 4121 ±0 0091 N=77	0 3803 ◊◊ ±0 0094 N=69
Relative Brain Weight (% of sacrifice weight)[a]							
	3 2109 ΓΓΓ ±0 0537 ßßß N=84	3 2069 ±0.0439 N=82[c]	3 2599 ±0 0455 N=80	3 1779 ±0 0589 N=71[b,c]	3 0921 ±0 0413 N=83	3 3676 ◊ ±0 0582 N=76[e]	3 8036 ◊◊◊ ±0.0883 N=69
Relative Paired Ovary Weight (% of sacrifice weight)[a]							
	0.0785 ±0.0022 N=84	0 0770 ±0 0022 N=82[f]	0 0795 ±0 0022 N=80	0 0772 ±0.0019 N=73	0 0806 ±0 0021 N=83	0 0821 ±0 0029 N=77	0 0827 ±0.0031 N=69
Relative Uterus Weight (% of sacrifice weight)[a]							
	0.1740 ±0 0104 N=84	0 1557 ±0.0078 N=83	0 1816 ±0 0083 N=80	0 1686 ±0 0077 N=73	0 1773 ±0 0073 N=83	0 1893 ±0 0097 N=77	0.1712 ±0 0102 N=68[g]

[a]Reported as the mean ± S E M (adjusted for intralitter correlations).
[b]Decrease in N is due to one or more weights being statistical outliers and therfore they were excluded
[c]Decrease in N is due to one or more weights being unrealistic and therfore they were excluded
[d]Decrease in N is due to one or more seminal vesicle weights inadvertently not being recorded
[e]Decrease in N is due to one brain weight inadvertently not being recorded
[f]Decrease in N is due to one paired ovary weight inadvertently not being recorded.
[g]Decrease in N is due to one uterus weight inadvertently not being recorded.
Γp<0.05, Overall analysis of correlated data.
ΓΓp<0 01, Overall analysis of correlated data
ΓΓΓp<0 001, Overall analysis of correlated data
ßp<0 05, Test for Linear Trend on correlated data
ßßp<0 01; Test for Linear Trend on correlated data.
ßßßp<0 001, Test for Linear Trend on correlated data
◊p<0 05, Pairwise comparison of correlated data
◊◊p<0.01; Pairwise comparison of correlated data
◊◊◊p<0 001, Pairwise comparison of correlated data

Table 84 Summary and Statistical Analysis of the F_2 Male Body Weights and Weight Changes During the Post-Mating Holding Period
(page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75.000	750.000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 84) (g)[a]							
	545 1 ‡‡‡ ± 8 5 §§§ N=30	554.5 ± 8.0 N=30	525 6 ± 9 4 N=30	528.6 ± 9 0 N=30	522 3 ± 7 7 N=30	483.8 *** ± 6 6 N=29[b]	390.2 *** ± 7 2 N=28[c]
Body Weight (sd 91) (g)[a]							
	560 3 ‡‡‡ ± 8.9 §§§ N=30	567 1 ± 8 3 N=30	537 4 ± 9 8 N=30	540 4 ± 9.4 N=30	533 6 ± 7.9 N=30	493 0 *** ± 7 6 N=29	399 8 *** ± 7 5 N=28
Body Weight (sd 98) (g)[a]							
	569 6 ‡‡‡ ± 9 4 §§§ N=30	577 1 ± 8.5 N=30	546 6 ± 10 1 N=30	551 4 ± 9 5 N=30	545 0 ± 8 2 N=30	499.4 *** ± 8.0 N=29	406.5 *** ± 7 3 N=28
Body Weight (sd 105) (g)[a]							
	584 3 ‡‡‡ ± 9 8 §§§ N=30	587.2 ± 8.8 N=30	559 0 ± 10.9 N=30	565.1 ± 9 7 N=30	557 0 ± 8 5 N=30	512.9 *** ± 8 4 N=29	414.0 *** ± 7 2 N=28
Body Weight Change (sd 84 to 91) (g)[a]							
#	15 3 ± 1 2 ¥¥ N=30	12.6 ± 1 4 N=30	11 9 ± 1 0 N=30	11.8 ± 1.1 N=30	11 3 ± 0 9 N=30	9.2 ± 2 2 N=29	9 6 ± 1.2 N=28

(continued)

Table 84 Summary and Statıstical Analysıs of the F_2 Male Body Weıghts and Weight Changes During the Post-Matıng Holdıng Period (page 2 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Body Weıght Change (sd 91 to 98) (g)[a]							
	9 3 ‡ ± 1 3 § N=30	10 0 ± 0 8 N=30	9 2 ± 1 1 N=30	11 0 ± 1 0 N=30	11 3 ± 1 0 N=30	6 5 ± 1.7 N=29	6 7 ± 1 1 N=28
Body Weıght Change (sd 98 to 105) (g)[a]							
#	14 6 ¶¶ ± 1 2 ¥ N=30	10 1 ± 1 8 N=30	12 4 ± 1 1 N=30	13 7 ± 0 9 N=30	12 1 ± 0 9 N=30	13.5 ± 1 0 N=29	7 5 ¤¤¤ ± 1 7 N=28

[a]Reported as the mean ± S E M , sd=study day with study day 0 beıng the first day of the prebreed period
[b]Decrease ın N ıs due to male 2365 being euthanized morıbund on study day 63
[c]Decrease ın N ıs due to male 2265 beıng found dead on study day -8 and male 2377 beıng found dead on study day -9
#Bartlett's test for homogeneıty of variances was significant (p<0 001) or could not be done because there was zero varıance ın one or more groups, therefore nonparametrıc statistical procedures were employed
‡p<0 05, ANOVA Test.
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Lınear Trend
§§§p<0 001; Test for Lınear Trend
***p<0 001, Dunnett's Test.
¶¶p<0 01, Kruskal-Wallıs Test
¥p<0.05, Jonckheere's Test
¥¥p<0 01, Jonckheere's Test
¤¤¤p<0 001, Mann-Whitney U Test

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 1 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
No Males at Terminal Sacrifice	30	30	30	30	30	29[a]	28[b]
Sacrifice Body Weight (g)[c]	591 54 ‡‡‡ ± 11 09 §§§ N=30	596 25 ± 9 56 N=30	568 71 ± 10 81 N=30	575 63 ± 10 14 N=30	567 07 ± 8.67 N=30	522 97 *** ± 8 62 N=28[d]	419.29 *** ± 7.05 N=28
Liver Weight (g)[c] #	23 3845 ¶¶¶ ± 0.7450 ¥¥¥ N=30	23.6761 ± 0 5599 N=30	21 7290 ¤ ± 0 4200 N=30	22 1571 ± 0 5727 N=30	21 8029 ± 0 3985 N=30	19 3143 ¤¤¤ ± 0 5006 N=29	15 8095 ¤¤¤ ± 0.3636 N=28
Paired Kidney Weight (g)[c]	4 3817 ‡‡‡ ± 0 1007 §§§ N=30	4 4047 ± 0 0715 N=30	4 2542 ± 0 0712 N=30	4 2059 ± 0 0703 N=30	4 2019 ± 0 0579 N=30	4 0827 * ± 0 0949 N=29	3.6338 *** ± 0 0849 N=28
Paired Adrenal Weight (g)[c]	0 0639 ± 0 0016 § N=29[e]	0.0639 ± 0 0021 N=30	0 0641 ± 0 0025 N=30	0 0637 ± 0.0020 N=30	0 0663 ± 0 0023 N=30	0.0601 ± 0 0019 N=28[e]	0 0593 ± 0 0022 N=28
Spleen Weight (g)[c]	0 9135 ‡‡‡ ± 0 0226 §§§ N=30	0 9110 ± 0 0217 N=29[e]	0 8699 ± 0 0304 N=30	0 8988 ± 0.0243 N=29[e]	0.8128 * ± 0 0256 N=29[e]	0 8006 ** ± 0.0256 N=29	0 7050 *** ± 0 0206 N=28
Brain Weight (g)[c]	2 1182 ‡‡‡ ± 0 0171 §§§ N=29[e]	2.1439 ± 0 0218 N=30	2.0978 ± 0 0217 N=30	2 1132 ± 0 0167 N=30	2 1016 ± 0 0143 N=30	2 0676 ± 0.0237 N=29	1.9699 *** ± 0.0216 N=28

(continued)

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 2 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[c]							
	0 0179 ‡ ± 0.0005 §§ N=29[f]	0.0177 ± 0 0003 N=30	0 0170 ± 0 0004 N=29[f]	0 0169 ± 0.0003 N=30	0 0167 ± 0 0005 N=26[f]	0 0167 ± 0 0003 N=27[e,f]	0 0158 ** ± 0 0004 N=26[f]
Paired Testes Weight (g)[c]							
	3 7050 ‡‡‡ ± 0 0484 §§§ N=30	3 5947 ± 0 0446 N=30	3.4845 * ± 0 0467 N=30	3 6570 ± 0 0578 N=30	3.6699 ± 0 0697 N=30	3 4859 * ± 0 0483 N=29	3 2689 *** ± 0.0506 N=28
Paired Epididymis Weight (g)[c]							
	1 4539 ‡‡‡ ± 0 0310 §§§ N=30	1 4066 ± 0 0309 N=29[e]	1 3972 ± 0 0198 N=30	1 4493 ± 0 0174 N=30	1 4063 ± 0 0194 N=30	1 3910 ± 0 0187 N=29	1.3119 *** ± 0 0220 N=28
Prostate Weight (g)[c]							
	0 6476 ‡‡ ± 0 0272 §§§ N=30	0 6161 ± 0 0219 N=30	0 5875 ± 0 0296 N=30	0 6359 ± 0 0219 N=30	0 6026 ± 0.0293 N=30	0 5811 ± 0 0245 N=28[e]	0 4910 *** ± 0.0244 N=27[e]
Seminal Vesicles with Coagulating Gland Weight (g)[c]							
	2 2911 ‡‡‡ ± 0.0719 §§§ N=30	2.1189 ± 0 0477 N=30	2 1828 ± 0 0561 N=30	2.3424 ± 0 0690 N=30	2 0945 ± 0 0687 N=30	2 2223 ± 0 0508 N=28[e]	1.7648 *** ± 0 0668 N=28
Preputial Gland Weight (g)[c]							
	0 2208 ± 0.0128 § N=30	0 2162 ± 0 0132 N=30	0 2205 ± 0 0141 N=30	0.2109 ± 0 0119 N=30	0 1959 ± 0 0137 N=29[g]	0 2048 ± 0 0125 N=29	0 1770 ± 0 0080 N=28

(continued)

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 3 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Liver Weight (% sacrifice weight)[c]							
	3 9324 ‡ ± 0 0684 N=30	3.9679 ± 0.0605 N=30	3 8266 ± 0 0443 N=30	3 8431 ± 0 0592 N=30	3 8499 ± 0 0529 N=30	3 6896 * ± 0 0617 N=28[d]	3 7770 ± 0 0707 N=28
Relative Paired Kidney Weight (% sacrifice weight)[c]							
#	0 7399 ¶¶¶ ± 0 0077 ¥¥¥ N=30	0 7410 ± 0 0109 N=30	0 7503 ± 0 0086 N=30	0 7327 ± 0 0090 N=30	0 7424 ± 0 0068 N=30	0 7827 ¤ ± 0 0146 N=28[d]	0 8663 ¤¤¤ ± 0 0144 N=28
Relative Paired Adrenal Weight (% sacrifice weight)[c]							
	0 0110 ‡‡‡ ± 0.0003 §§§ N=29[e]	0 0108 ± 0 0004 N=30	0 0113 ± 0 0004 N=30	0 0111 ± 0 0003 N=30	0.0117 ± 0.0004 N=30	0 0117 ± 0.0004 N=27[d,e]	0.0143 *** ± 0 0006 N=28
Relative Spleen Weight (% sacrifice weight)[c]							
	0 1552 ‡‡ ± 0 0040 §§§ N=30	0 1525 ± 0 0039 N=29[e]	0 1526 ± 0 0034 N=30	0 1564 ± 0 0035 N=29[e]	0 1433 ± 0 0036 N=29[e]	0 1544 ± 0.0047 N=28[d]	0 1683 ± 0.0042 N=28
Relative Brain Weight (% sacrifice weight)[c]							
	0 3617 ‡‡‡ ± 0.0074 §§§ N=29[e]	0 3619 ± 0 0064 N=30	0 3715 ± 0.0057 N=30	0 3699 ± 0.0062 N=30	0 3733 ± 0 0065 N=30	0 3978 ** ± 0.0061 N=28[d]	0 4730 *** ± 0.0089 N=28
Relative Pituitary Weight (% sacrifice weight)[c]							
	0 0030 ‡‡‡ ± 0.0001 §§§ N=29[f]	0.0030 ± 0.0001 N=30	0.0030 ± 0.0001 N=29[f]	0 0029 ± 0.0001 N=30	0.0030 ± 0.0001 N=26[f]	0 0032 ± 0.0001 N=26[d,e,f]	0 0038 *** ± 0.0001 N=26[f]

(continued)

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 4 of 6)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Relative Paired Testes Weight (% sacrifice weight)[c]							
	0 6313 ‡‡‡ ± 0 0119 §§§ N=30	0 6077 ± 0 0128 N=30	0 6170 ± 0 0109 N=30	0.6395 ± 0 0125 N=30	0 6493 ± 0 0118 N=30	0 6697 ± 0 0103 N=28[d]	0 7836 *** ± 0 0144 N=28
Relative Paired Epididymis Weight (% sacrifice weight)[c]							
	0 2469 ‡‡‡ ± 0 0051 §§§ N=30	0 2376 ± 0.0064 N=29[e]	0 2476 ± 0 0049 N=30	0 2534 ± 0.0042 N=30	0 2493 ± 0 0044 N=30	0 2676 * ± 0 0044 N=28[d]	0 3136 *** ± 0 0044 N=28
Relative Prostate Weight (% sacrifice weight)[c]							
	0 1105 ± 0 0052 N=30	0.1035 ± 0 0036 N=30	0.1034 ± 0 0050 N=30	0 1110 ± 0.0038 N=30	0 1060 ± 0 0047 N=30	0 1131 ± 0 0045 N=27[d,e]	0 1172 ± 0 0061 N=27[e]
Relative Seminal Vesicles with Coagulating Gland Weight (% sacrifice weight)[c]							
	0 3892 ‡‡‡ ± 0 0120 § N=30	0 3572 ± 0 0087 N=30	0.3870 ± 0 0114 N=30	0 4077 ± 0 0109 N=30	0.3713 ± 0 0128 N=30	0 4312 * ± 0 0119 N=27[d,e]	0 4207 ± 0 0153 N=28
Relative Preputial Gland Weight (% sacrifice weight)[c]							
	0 0376 ± 0 0022 § N=30	0.0365 ± 0 0023 N=30	0 0385 ± 0 0021 N=30	0 0366 ± 0.0020 N=30	0.0347 ± 0 0024 N=29[g]	0.0393 ± 0.0027 N=28[d]	0 0423 ± 0 0018 N=28
Percent Motile Sperm[c]							
#	79 0 ± 1 4 N=30	76.1 ± 2 9 N=30	76 8 ± 1 6 N=30	76 3 ± 2 1 N=30	77 0 ± 1 4 N=30	79 7 ± 1 2 N=29	78.6 ± 1 0 N=28

(continued)

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at
Evaluation (page 5 of 6)

	Bisphenol A (ppm in the feed)				
	0	0 015	0 3	4 5	75
Percent Progressively Motile Sperm[c]					
#	65 8 ± 1 4 N=30	64 1 ± 2 6 N=30	63 6 ± 1 9 N=30	63 6 ± 2 2 N=30	64 7 ± 1 6 N=30
Epididymal Sperm Concentration (mil/g)[c]					
	924.19 ± 25 22 N=30	908 42 ± 35 65 N=30	907 95 ± 28 28 N=30	894 06 ± 24 36 N=30	860 14 ± 31 97 N=30
Spermatid Head Concentration (mil/g)[c]					
	91 86 ± 5 30 N=30	81 30 ± 6 17 N=30	95 28 ± 6 06 N=30	90 38 ± 6 24 N=30	93 00 ± 5 40 N=30
Daily Sperm Production per Testis[c]					
	37 15 ± 2 12 N=30	32 30 ± 2 50 N=30	36 17 ± 2 24 N=30	36 14 ± 2 62 N=30	36 61 ± 1 85 N=30
Efficiency of Daily Sperm Production[c]					
	19 93 ± 1.15 N=30	17 64 ± 1 34 N=30	20 67 ± 1 32 N=30	19 60 ± 1 35 N=30	20 17 ± 1 17 N=30
Percent Abnormal Sperm[c]					
#	2 19 ± 0 38 N=30	4 89 ± 2 99 N=30	4 10 ± 2 30 N=30	3 25 ± 1 39 N=30	3 47 ± 1 12 N=30

(continued)

Table 90 Summary and Statistical Analysis of the F_2 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 6 of 6)

[a]Male 2365 was euthanized moribund on study day 63
[b]Male 2265 was found dead on study day -8 and male 2377 was found dead on study day -9
[c]Reported as the mean ± S E M
[d]Decrease in N is due to the sacrifice weight inadvertently not being recorded for one male
[e]Decrease in N is due to one weight being a statistical outlier and therefore it was removed
[f]Decrease in N is due to the pituitary inadvertently not being saved for one or more males
[g]Decrease in N is due to the preputial gland weight for one male inadvertently not being recorded
[#]Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.
‡p<0 05, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0.01, Dunnett's Test
***p<0 001, Dunnett's Test
¶¶¶p<0 01, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test.
¤p<0 05, Mann-Whitney U Test
¤¤¤p<0 001, Mann-Whitney U Test

[redacted]

Table 92 Summary and Statıstıcal Analysıs of the F_2 Female Organ Weights and Relative Organ Weıghts at Scheduled Sacrifice, Paıred Ovarian Follicle Counts and Vagınal Cytology at Necropsy (page 1 of 5)

	Bisphenol A (ppm ın the feed)						
	0	0 015	0.3	4 5	75	750	7500
No Females at Scheduled Sacrıfice	30	30	30	30	30	30	28[a,b]
Sacrıfice Body Weıght (g)[c]							
	329 6 ‡‡‡ + 5 2 §§§ N=30	338.7 + 3 9 N=30	326 4 + 5 9 N=30	322 0 + 5 9 N=30	326 2 + 4.8 N=29[d]	321.2 + 5 8 N=30	282 1 *** + 4.0 N=28
Lıver Weıght (g)[c]							
	16 8719 ‡‡‡ + 0 3612 N=30	19 9438 *** + 0 5596 N=30	16 5695 + 0 3568 N=30	16.4520 + 0 4593 N=30	16.9757 + 0 5096 N=30	16 9027 + 0 4870 N=30	17 3374 + 0 5079 N=28
Paıred Kıdney Weight (g)[c]							
	2 9352 ‡‡‡ + 0 0493 §§§ N=30	2.9827 + 0 0412 N=30	2 8673 + 0 0454 N=30	2 8171 + 0 0392 N=30	2.8508 + 0.0489 N=30	2 8105 + 0 0601 N=30	2.6591 *** + 0.0530 N=28
Paired Adrenal Weıght (g)[c]							
	0 0905 ‡‡‡ + 0 0017 §§§ N=30	0 0895 + 0 0023 N=30	0 0832 + 0 0027 N=29[e]	0 0833 + 0.0029 N=30	0 0893 + 0 0025 N=30	0 0853 + 0 0021 N=30	0 0743 *** + 0 0020 N=28
Spleen Weıght (g)[c]							
	0.5936 ‡‡ + 0 0124 N=29[e]	0 6163 + 0 0139 N=30	0 6161 + 0 0134 N=30	0 6151 + 0 0137 N=29[e]	0 5458 + 0 0147 N=30	0.5835 + 0 0183 N=30	0 5698 + 0 0190 N=28
Braın Weight (g)[c]							
#	1 8841 ¶ + 0 0207 N=30	1 8719 + 0 0140 N=30	1.9103 + 0.0317 N=29[f]	1 8550 + 0 0232 N=30	1 9286 + 0 0197 N=30	1 9248 + 0 0158 N=30	1 8211 + 0.0273 N=28

(continued)

Table 92 Summary and Statistical Analysis of the F_2 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4.5	75	750	7500
Pituitary Weight (g)[c]							
	0 0195 ‡‡‡ ± 0 0005 §§§ N=30	0 0189 ± 0 0005 N=30	0 0184 ± 0 0006 N=29[g]	0 0186 ± 0 0004 N=30	0 0188 ± 0 0005 N=29[g]	0 0181 ± 0 0006 N=29[h]	0.0149 *** ± 0.0004 N=28
Paired Ovary Weight (g)[c]							
	0 1753 ‡‡‡ ± 0 0054 §§§ N=30	0 1541 * ± 0 0050 N=30	0 1605 ± 0 0050 N=30	0 1471 *** ± 0 0064 N=30	0 1548 * ± 0 0037 N=30	0 1576 ± 0 0045 N=30	0 1152 *** ± 0 0043 N=28
Uterus Weight (g)[c]							
#	0 8888 ¶¶ ± 0 1599 ¥ N=30	0 7846 ± 0 0448 N=30	0 6806 ± 0 0296 N=30	0 6958 ± 0 0385 N=30	0 7475 ± 0 0428 N=30	0.7577 ± 0 0366 N=30	0 5778 ¤ ± 0 0240 N=28
Relative Liver Weight (% sacrifice weight)[c]							
	5 1272 ‡‡‡ ± 0 0908 §§§ N=30	5 9202 *** ± 0 1911 N=30	5 1003 ± 0 1105 N=30	5 1405 ± 0 1478 N=30	5 2111 ± 0 1429 N=29[d]	5 2809 ± 0 1482 N=30	6 1237 *** ± 0 1326 N=28
Relative Paired Kidney Weight (% sacrifice weight)[c]							
	0 8926 ‡‡ ± 0.0126 §§§ N=30	0 8814 ± 0 0098 N=30	0 8820 ± 0 0129 N=30	0 8795 ± 0 0135 N=30	0 8735 ± 0 0133 N=29[d]	0 8760 ± 0 0129 N=30	0.9426 * ± 0.0140 N=28
Relative Paired Adrenal Weight (% sacrifice weight)[c]							
	0 0277 ± 0 0007 N=30	0 0265 ± 0.0007 N=30	0 0257 ± 0 0010 N=29[e]	0 0262 ± 0 0011 N=30	0 0273 ± 0 0009 N=29[d]	0 0267 ± 0 0007 N=30	0 0263 ± 0 0007 N=28

(continued)

Table 92 Summary and Statistical Analysis of the F_2 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0.3	4 5	75	750	7500
Relative Spleen Weight (% sacrifice weight)[c]							
	0 1823 ‡‡‡ ± 0 0041 §§§ N=29[e]	0 1823 ± 0 0041 N=30	0 1891 ± 0 0030 N=30	0 1922 ± 0 0039 N=29[e]	0 1667 * ± 0.0040 N=29[d]	0 1817 ± 0 0047 N=30	0 2015 ** ± 0 0054 N=28
Relative Brain Weight (% sacrifice weight)[c]							
	0 5760 ‡‡‡ ± 0 0116 §§§ N=30	0 5550 ± 0 0082 N=30	0.5918 ± 0.0129 N=29[f]	0 5804 ± 0.0109 N=30	0 5937 ± 0 0102 N=29[d]	0 6033 ± 0 0091 N=30	0.6492 *** ± 0 0140 N=28
Relative Pituitary Weight (% sacrifice weight)[c]							
	0 0059 ± 0 0002 §§ N=30	0.0056 ± 0 0001 N=30	0 0057 ± 0 0002 N=29[g]	0 0058 ± 0.0001 N=30	0 0058 ± 0 0002 N=28[d,g]	0 0056 ± 0.0002 N=29[h]	0 0053 ± 0 0001 N=28
Relative Paired Ovary Weight (% sacrifice weight)[c]							
	0 0536 ‡‡‡ ± 0.0019 §§§ N=30	0 0455 ** ± 0.0014 N=30	0 0494 ± 0.0015 N=30	0.0463 ** ± 0 0021 N=30	0 0476 * ± 0.0013 N=29[d]	0.0492 ± 0 0013 N=30	0 0409 *** ± 0 0015 N=28
Relative Uterus Weight (% sacrifice weight)[c]							
#	0 2622 ± 0.0386 N=30	0 2329 ± 0 0139 N=30	0.2104 ± 0 0099 N=30	0 2178 ± 0 0122 N=30	0 2303 ± 0 0135 N=29[d]	0.2383 ± 0.0123 N=30	0 2051 ± 0 0083 N=28

(continued)

Table 92 Summary and Statistical Analysis of the F_2 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Paired Ovarian Follicle Count[c,i]							
	409 2 ± 32 7 N=10						378 0 ± 25.5 N=10
VAGINAL CYTOLOGY EVALUATION AT NECROPSY[j]							
No Females Evaluated	30	30	29[k]	29[k]	30	30	28[a,b]
No in Proestrus	2	6	1	3	4	3	0
% in Proestrus	7.14	20 00	3 45	10 34	13 33	10 71	0 00
No in Estrus	8 ££	6	9	5	13	11	0 Φ
% in Estrus	28 57	20 00	31.03	17 24	43 33	39 29	0 00
No in Metestrus	3	1	4	3	2	0	1
% in Metestrus	10 71	3 33	13 79	10 34	6 67	0 00	3.70
No in Diestrus	15 ££	17	15	18	11	14	26 ΦΦ
% in Diestrus	53.57	56 67	51 72	62 07	36.67	50 00	96.30
No Stage Not Determined	2	0	0	0	0	2	1
No No Cells Present	0	0	0	0	0	0	0

(continued)

Table 92 Summary and Statistical Analysis of the F_2 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 5)

[a]Female 2058 was found dead on study day -7
[b]Female 2354 was found dead on study day -8
[c]Reported as the mean ± S E M
[d]Decrease in N is due to the sacrifice weight for one female inadvertently not being recorded
[e]Decrease in N is due to one weight being a statistical outlier and therefore it was removed
[f]Decrease in N is due to one weight being unrealistic and therefore it was excluded
[g]Decrease in N is due to the pituitary inadvertently not being saved for one female
[h]Decrease in N is due to the pituitary gland not being present in the head at the time of weighing
[i]Ovarian follicle counts were done for 10 control females and 10 females in the 7500.000 ppm Bisphenol A dose group
[j]For 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, metestrus/estrus and estrus/diestrus 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
[k]Vaginal smear for one or more females inadvertently not done
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test.
**p<0 01, Dunnett's Test
***p<0 001; Dunnett's Test
¶p<0 05, Kruskal-Wallis Test
¶¶p<0 01, Kruskal-Wallis Test
¥p<0 05; Jonckheere's Test
¤p<0 05; Mann-Whitney U Test
££p<0 01, Chi-Square Test
Φp<0 05, Fisher Exact Test
ΦΦp<0 01, Fisher Exact Test

Table 95 Summary and Statistical Analysis of the F_3 Female Vaginal Opening and the F_3 Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75 000	750 000	7500 000
No of Females Evaluated	30	30	30	30	30	30	30
Day of Vaginal Opening[a]							
	31 3 ‡‡‡ ± 0 3 §§§ N=30	31 1 ± 0 3 N=30	31 1 ± 0 3 N=30	31 1 ± 0 5 N=30	31 6 ± 0 3 N=30	30 9 ± 0 3 N=30	33.8 *** ± 0 5 N=30
Body Weight (g) on Day of Acquisition[a]							
	105 59 ± 2 38 § N=30	106 30 ± 2 48 N=30	101 85 ± 2 23 N=30	105 64 ± 2 85 N=30	105 15 ± 1 98 N=30	102 41 ± 1 86 N=30	99 04 ± 2 48 N=30
Adjusted Day of Vaginal Opening[b]							
	31 1 δδδ ± 0 3 λλλ N=30	30 8 ± 0 3 N=30	31 3 ± 0 3 N=30	30 9 ± 0.3 N=30	31 4 ± 0 3 N=30	31 1 ± 0 3 N=30	34.3 φφφ ± 0 3 N=30
No of Males Evaluated	30	30	29[c]	30	30	30	30
Day of Preputial Separation[a]							
	42 1 ‡‡‡ ± 0 4 §§§ N=30	42.2 ± 0 3 N=30	43 1 ± 0 4 N=28[d]	41.9 ± 0 4 N=30	42.8 ± 0.3 N=30	43 1 ± 0.2 N=30	45.2 *** ± 0 4 N=30
Body Weight *(g) on Day of Acquisition*[a]							
	209 33 ‡‡‡ ± 3 39 §§§ N=30	214 40 ± 3 26 N=29[e]	208 32 ± 4 05 N=28[e]	208.37 ± 3 37 N=29[e]	214.31 ± 3 48 N=30	210 48 ± 3 34 N=30	186 76 *** ± 2 59 N=30

(continued)

Table 95 Summary and Statistical Analysis of the F_3 Female Vaginal Opening and the F_3 Male Preputial Separation Data (page 1 of 2)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4.500	75 000	750 000	7500 000
Adjusted Day of Preputial Separation[b]							
	42 0 δδδ ± 0 3 λλλ N=30	42 0 ± 0 3 N=30	43 1 ± 0 3 N=28[d]	41 9 ± 0 3 N=30	42 6 ± 0 3 N=30	43 0 ± 0 3 N=30	46 0 φφφ ± 0 4 N=30

[a]Reported as the mean ± S E M with day being postnatal day
[b]Reported as the adjusted mean (body weight as covariate) ± S.E M , pnd=postnatal day
[c]Male 3095 was found dead on study day -5 during the holding period after weaning and prior to the start of the prebreed period
[d]Decrease in N is due to the fact that the day that male 3347 was positive was inadvertently not recorded
[e]Decrease in N is due to the body weight for one male inadvertently not being recorded
‡‡‡p<0 001, ANOVA Test
§p<0.05, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
***p<0 001, Dunnett's Test
δδδp<0 001, Analysis of Covariance with body weight on day of acquisition as covariate
λλλp<0 001, Linear Trend Analysis of Covariance with body weight on day of acquisition as covariate
φφφp<0 001, Dunnett's Test with body weight on day of acquisition as covariate

Table 96 Summary and Statistical Analysis of the F_3 Male Body Weights and Weight Changes During the Post-Wean Holding Period (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750.000	7500 000
No Males on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]	121 0 ± 11 1 § N=30	128 1 ± 11 4 N=30	114 6 ± 9.5 N=29[b]	123 3 ± 10.3 N=30	119 3 ± 10 1 N=30	116 9 ± 9.5 N=30	93 6 ± 8.5 N=30
Body Weight (sd 7) (g)[a]	174 4 ± 12 7 §§ N=30	183 7 ± 12 5 N=30	167 8 ± 10 8 N=29	176 7 ± 11 4 N=30	172 9 ± 11 4 N=30	168 5 ± 10 4 N=30	136.1 ± 9 2 N=30
Body Weight (sd 14) (g)[a]	234 6 ‡‡ ± 12 8 §§§ N=30	242 5 ± 12 4 N=30	223 8 ± 11 4 N=29	234 8 ± 11 3 N=30	232 7 ± 11 5 N=30	225.6 ± 10.4 N=30	180 3 ** ± 8 9 N=30
Body Weight (sd 21) (g)[a]	287 6 ‡‡‡ ± 12 1 §§§ N=30	295 3 ± 11.4 N=30	278 0 ± 11 3 N=29	292 3 ± 11.1 N=30	289 2 ± 11 4 N=30	275 0 ± 9 6 N=30	220.8 *** ± 8 1 N=30
Body Weight (sd 28) (g)[a]	336 5 ‡‡‡ ± 10 2 §§§ N=30	345 5 ± 9 4 N=30	327 1 ± 10 1 N=29	342 6 ± 10 1 N=30	340 3 ± 10 2 N=30	321.1 ± 8 7 N=30	258 5 *** ± 7 5 N=30
Body Weight (sd 35) (g)[a]	378 7 ‡‡‡ ± 8 7 §§§ N=30	387 4 ± 8 4 N=30	369 0 ± 9 2 N=29	384 9 ± 9 0 N=30	384 1 ± 9 4 N=30	359 8 ± 7 5 N=30	286 8 *** ± 5 9 N=30

(continued)

Table 96 Summary and Statistical Analysis of the F_3 Male Body Weights and Weight Changes During the Post-Wean Holding Period
(page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75.000	750 000	7500 000
Body Weight (sd 42) (g)[a]							
	414 6 ‡‡‡	421 0	402 1	416 0	418 9	389 3	308 1 ***
	± 8 1 §§§	± 7 7	± 9 4	± 8 7	± 9 2	± 7 0	± 5 9
	N=30	N=30	N=29	N=30	N=30	N=30	N=30
Body Weight (sd 49) (g)[a]							
	443 4 ‡‡‡	450 6	431 4	446 4	453 6	415 4	326.4 ***
	± 7 6 §§§	± 7 7	± 9 0	± 8 2	± 9 7	± 7 1	± 5.6
	N=30	N=30	N=29	N=30	N=30	N=30	N=30
Body Weight (sd 56) (g)[a]							
	462 0 ‡‡‡	465.8	449 5	464 0	471 9	433 8	337.0 ***
	± 6 8 §§§	± 7 8	± 8 9	± 8 3	± 9 4	± 7 3	± 5 3
	N=30	N=30	N=29	N=30	N=30	N=30	N=30
Body Weight (sd 63) (g)[a]							
	481 2 ‡‡‡	485.8	471 1	485 9	494 9	454.6	354 8 ***
	± 6 8 §§§	± 8 3	± 8 5	± 7 9	± 9 3	± 7 8	± 5 0
	N=30	N=30	N=29	N=30	N=30	N=30	N=30
Body Weight (sd 70) (g)[a,c]							
	478 4	499 5	475 4	479 6	497 2	464.0	355 9
	± 10 9	± 11 7	± 13.7	± 9 3	± 12 6	± 13.4	± 4.4
	N=15	N=15	N=15	N=15	N=15	N=15	N=15
Body Weight Change (sd 0 to 7) (g)[a]							
	53.3 ‡‡‡	55 6	53 2	53 4	53 6	51.6	42.5 ***
	± 1 9 §§§	± 1 5	± 1 5	± 1 5	± 1.7	± 1 3	± 1 0
	N=30	N=30	N=29	N=30	N=30	N=30	N=30

(continued)

Table 96 Summary and Statistical Analysis of the F_3 Male Body Weights and Weight Changes During the Post-Wean Holding Period (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500.000
Body Weight Change (sd 7 to 14) (g)[a]	60 2 ‡‡‡ ± 1 7 §§§ N=30	58 8 ± 1 5 N=30	56 0 ± 1 6 N=29	58 1 ± 1 4 N=30	59 8 ± 1 1 N=30	57 1 ± 1 4 N=30	44.2 *** ± 1 2 N=30
Body Weight Change (sd 14 to 21) (g)[a]	53 0 ‡‡‡ ± 1 6 §§§ N=30	52 8 ± 2 0 N=30	54 2 ± 1 5 N=29	57 5 ± 1 5 N=30	56 5 ± 1.7 N=30	49 4 ± 1.7 N=30	40 5 *** ± 1 3 N=30
Body Weight Change (sd 21 to 28) (g)[a]	48 9 ‡‡‡ ± 2 8 §§§ N=30	50 3 ± 2 8 N=30	49 0 ± 2 5 N=29	50 3 ± 1 9 N=30	51 1 ± 2 4 N=30	46.1 ± 2 1 N=30	37 7 ** ± 1 5 N=30
Body Weight Change (sd 28 to 35) (g)[a]	42 1 ‡‡‡ ± 2.1 §§§ N=30	41.9 ± 2 6 N=30	42 0 ± 2 1 N=29	42 2 ± 2 0 N=30	43 8 ± 2 2 N=30	38 7 ± 1 9 N=30	28 3 *** ± 2.1 N=30
Body Weight Change (sd 35 to 42) (g)[a]	35 9 ‡‡‡ ± 1 6 §§§ N=30	33 6 ± 1 9 N=30	33 1 ± 2 2 N=29	31 1 ± 2.2 N=30	34 8 ± 1 8 N=30	29 5 ± 1 7 N=30	21 3 *** ± 1 4 N=30
Body Weight Change (sd 42 to 49) (g)[a] #	28 7 ¶¶¶ ± 1 4 ¥¥¥ N=30	29 5 ± 1 8 N=30	29 2 ± 1 6 N=29	30.4 ± 1 8 N=30	34 8 ± 3 6 N=30	26 1 ± 1 3 N=30	18 2 ¤¤¤ ± 1.3 N=30

(continued)

Table 96. Summary and Statistical Analysis of the F_3 Male Body Weights and Weight Changes During the Post-Wean Holding Period
(page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75 000	750 000	7500.000
Body Weight Change (sd 49 to 56) (g)[a]							
#	18 7 ¶¶¶ ± 1 4 ¥ N=30	15 3 ± 1 7 N=30	18 1 ± 1.1 N=29	17.7 ± 1 0 N=30	18 2 ± 3 6 N=30	18 5 ± 1 1 N=30	10 7 ¤¤¤ ± 1 2 N=30
Body Weight Change (sd 56 to 63) (g)[a]							
	19.2 ± 1.3 § N=30	19 9 ± 2 1 N=30	21 6 ± 1 5 N=29	21 9 ± 1 1 N=30	23 0 ± 1 3 N=30	20 8 ± 1 7 N=30	17 7 ± 1 3 N=30
Body Weight Change (sd 0 to 63) (g)[a]							
	360 2 ‡‡‡ ± 10.0 §§§ N=30	357 7 ± 13 2 N=30	356 5 ± 10 0 N=29	362 6 ± 8 1 N=30	375 5 ± 10 2 N=30	337 7 ± 10 3 N=30	261 2 *** ± 6.8 N=30
Body Weight Change (sd 63 to 70) (g)[a,c]							
	13 2 ± 3 9 N=15	16 2 ± 1.3 N=15	17 5 ± 0 9 N=15	15 5 ± 1.1 N=15	15 1 ± 2 6 N=15	16 0 ± 3 1 N=15	13 3 ± 1.1 N=15

(continued)

Table 96. Summary and Statistical Analysis of the F_3 Male Body Weights and Weight Changes During the Post-Wean Holding Period (page 5 of 5)

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the post-wean holding period

[b]Decrease in N is due to male 3095 being euthanized moribund on study day -5 (negative study days were during the holding period after weaning and prior to the start of the post-wean holding period)

[c]Males were scheduled for sacrifice over a two week period (cohort 1 the first week and cohort 2 the second week), therefore this endpoint includes only those males that were scheduled for sacrifice during the second week Statistical analyses were not performed on these endpoints since not all males were represented

[c]Males were scheduled for sacrifice over a two week period (cohort 1 the first week and cohort 2 the second week), therefore this endpoint includes only those males that were scheduled for sacrifice during the second week

[#]Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed

‡‡p<0 01, ANOVA Test

‡‡‡p<0 001, ANOVA Test

§p<0 05, Test for Linear Trend

§§p<0 01, Test for Linear Trend

§§§p<0 001, Test for Linear Trend

**p<0 01, Dunnett's Test

***p<0 001, Dunnett's Test

¶¶¶p<0 001, Kruskal-Wallis Test

¥p<0 05, Jonckheere's Test

¥¥¥p<0.001, Jonckheere's Test

¤¤¤p<0 001, Mann-Whitney U Test

Table 99. Summary and Statistical Analysis of the F_3 Female Body Weights and Weight Changes During the Post-Wean Holding Period (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0.300	4 500	75 000	750 000	7500.000
No Females on Study	30	30	30	30	30	30	30
Body Weight (sd 0) (g)[a]							
	103 5 ± 8 4 § N=30	108.3 ± 8 5 N=30	100 4 ± 8 0 N=30	105 9 ± 8 5 N=30	100 3 ± 7 3 N=30	100.8 ± 6 9 N=30	82.0 ± 6.9 N=30
Body Weight (sd 7) (g)[a]							
	140 1 ‡ ± 7 4 §§§ N=30	144 0 ± 7 1 N=30	133 1 ± 6 6 N=30	140 7 ± 7 4 N=30	135 1 ± 6 3 N=30	136 6 ± 5 4 N=30	112 9 * ± 6 0 N=30
Body Weight (sd 14) (g)[a]							
	173.7 ‡‡‡ ± 6 0 §§§ N=30	178 0 ± 6 0 N=30	166 2 ± 5 7 N=30	171 7 ± 6.6 N=30	168 4 ± 5 1 N=30	169 2 ± 3 9 N=30	142 1 *** ± 5.0 N=30
Body Weight (sd 21) (g)[a]							
	199 0 ‡‡‡ ± 5.5 §§§ N=30	203 0 ± 5 5 N=30	191 0 ± 5 8 N=30	197 0 ± 6 3 N=30	194 0 ± 4 4 N=30	192 8 ± 3 6 N=30	162 6 *** ± 4 4 N=30
Body Weight (sd 28) (g)[a]							
	218 5 ‡‡‡ ± 4 9 §§§ N=30	223.8 ± 5 6 N=30	213 5 ± 5.5 N=30	217.0 ± 5.6 N=30	216 8 ± 3 8 N=30	214 2 ± 3 5 N=30	179.8 *** ± 4.3 N=30
Body Weight (sd 35) (g)[a]							
	234 9 ‡‡‡ ± 4 2 §§§ N=30	245 4 ± 4 0 N=30	229 2 ± 5 6 N=30	235 3 ± 5 8 N=30	233 6 ± 3 9 N=30	229.2 ± 3.7 N=30	189.1 *** ± 3.4 N=30

(continued)

Table 99 Summary and Statistical Analysis of the F_3 Female Body Weights and Weight Changes During the Post-Wean Holding Period
(page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500.000
Body Weight (sd 42) (g)[a]							
	250 0 ‡‡‡ ± 4 3 §§§ N=30	260 8 ± 4 0 N=30	243.9 ± 6 0 N=30	249 7 ± 5.7 N=30	247 7 ± 3 8 N=30	242 8 ± 4 0 N=30	200 7 *** ± 4 2 N=30
Body Weight (sd 49) (g)[a]							
	259 7 ‡‡‡ ± 4 2 §§§ N=30	269 9 ± 4.0 N=30	254 8 ± 6 0 N=30	258 7 ± 5 4 N=30	257 7 ± 3 8 N=30	254 3 ± 4.3 N=30	208 5 *** ± 4 5 N=30
Body Weight (sd 56) (g)[a]							
	267 0 ‡‡‡ ± 4 2 §§§ N=30	280 8 ± 4 0 N=30	263 9 ± 5 7 N=30	268 7 ± 5 5 N=30	266 5 ± 3 3 N=30	261 9 ± 4 6 N=30	215 5 *** ± 4 0 N=30
Body Weight (sd 63) (g)[a]							
	274 1 ‡‡‡ ± 4 3 §§§ N=30	288 8 ± 4 6 N=30	272 7 ± 6.2 N=30	276 7 ± 5 5 N=30	277 0 ± 3 5 N=30	270 1 ± 5 0 N=30	221 3 *** ± 4 5 N=30
Body Weight (sd 70) (g)[a]							
	279.3 ‡‡‡ ± 4 3 §§§ N=30	291 1 ± 4 4 N=30	276 7 ± 6 1 N=30	281 4 ± 5 6 N=30	283 2 ± 3 8 N=30	274 3 ± 4 7 N=30	228 0 *** ± 4 4 N=30
Body Weight (sd 77) (g)[a]							
	284 5 ‡‡‡ ± 4 3 §§§ N=30	297 9 ± 4 0 N=30	282 5 ± 6 0 N=30	286 3 ± 5 5 N=30	289 7 ± 3.5 N=30	280 0 ± 5 1 N=30	230.9 *** ± 4 9 N=30

(continued)

Table 99 Summary and Statistical Analysis of the F_3 Female Body Weights and Weight Changes During the Post-Wean Holding Period (page 3 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750 000	7500 000
Body Weight (sd 84) (g)[a,b]							
	282.2 ± 4 8 N=15	308 9 ± 4.9 N=15	284 7 ± 9 6 N=15	281 2 ± 3 6 N=15	291 2 ± 5 8 N=15	300 7 ± 7 1 N=15	228 7 ± 4 0 N=15
Body Weight Change (sd 0 to 7) (g)[a]							
#	36 6 ± 1 6 N=30	35 6 ± 1 8 N=30	32 7 ± 3 4 N=30	34 8 ± 1 7 N=30	34 8 ± 1 3 N=30	35 7 ± 1 9 N=30	30.9 ± 1 4 N=30
Body Weight Change (sd 7 to 14) (g)[a]							
	33 6 ± 2 0 N=30	34 0 ± 1 8 N=30	33 1 ± 1 8 N=30	31.0 ± 1 8 N=30	33 4 ± 1 9 N=30	32 6 ± 2 1 N=30	29 2 ± 1 7 N=30
Body Weight Change (sd 14 to 21) (g)[a]							
	25 3 ± 1 1 §§ N=30	25 0 ± 1 2 N=30	24 7 ± 1 6 N=30	25 3 ± 1 1 N=30	25 6 ± 1 2 N=30	23 6 ± 1 4 N=30	20 5 ± 1 3 N=30
Body Weight Change (sd 21 to 28) (g)[a]							
#	19 6 ± 1 6 N=30	20 8 ± 3.4 N=30	22 5 ± 1.6 N=30	20 0 ± 1.3 N=30	22 7 ± 1 3 N=30	21.4 ± 1 8 N=30	17 2 ± 1.0 N=30
Body Weight Change (sd 28 to 35) (g)[a]							
#	16 4 ¶¶¶ ± 1 5 ¥¥¥ N=30	21 5 ± 3 4 N=30	15 7 ± 1 0 N=30	18 3 ± 1 1 N=30	16.8 ± 0 9 N=30	14 9 ± 1 0 N=30	9.3 ¤¤¤ ± 1 5 N=30

(continued)

Table 99 Summary and Statistical Analysis of the F_3 Female Body Weights and Weight Changes During the Post-Wean Holding Period (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0.300	4 500	75 000	750 000	7500 000
Body Weight Change (sd 35 to 42) (g)[a]							
#	15 0 ± 1 2 ¥ N=30	15.5 ± 1 3 N=30	14 7 ± 1 3 N=30	14 4 ± 1 3 N=30	14 2 ± 1 1 N=30	13 7 ± 1.4 N=30	11 6 ± 2 3 N=30
Body Weight Change (sd 42 to 49) (g)[a]							
	9 7 ± 1 1 N=30	9 1 ± 1 0 N=30	10 8 ± 1 1 N=30	9 0 ± 0 9 N=30	10 0 ± 1 2 N=30	11 5 ± 1 1 N=30	7.7 ± 1.0 N=30
Body Weight Change (sd 49 to 56) (g)[a]							
	7 3 ± 1 5 N=30	10 9 ± 1 7 N=30	9 2 ± 1 4 N=30	10.0 ± 1 2 N=30	8.7 ± 1 2 N=30	7.6 ± 1 2 N=30	7 0 ± 1 2 N=30
Body Weight Change (sd 56 to 63) (g)[a]							
	7 1 ± 1 3 N=30	8 1 ± 1 8 N=30	8 7 ± 1 6 N=30	8 0 ± 1 3 N=30	10 6 ± 1 7 N=30	8 1 ± 1 3 N=30	5 8 ± 1 1 N=30
Body Weight Change (sd 63 to 70) (g)[a]							
	5.2 ± 1 0 N=30	2 2 ± 1 4 N=30	4 0 ± 1 5 N=30	4 7 ± 1 1 N=30	6 2 ± 1 5 N=30	4.3 ± 1 2 N=30	6 7 ± 1.0 N=30
Body Weight Change (sd 70 to 77) (g)[a]							
	5 2 ± 1.0 § N=30	6 8 ± 1 3 N=30	5 8 ± 1 1 N=30	4 9 ± 1.2 N=30	6 4 ± 1 3 N=30	5 7 ± 1 1 N=30	2 9 ± 1 1 N=30

[redacted]

(continued)

Table 99 Summary and Statistical Analysis of the F_3 Female Body Weights and Weight Changes During the Post-Wean Holding Period
(page 5 of 5)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75 000	750 000	7500.000
Body Weight Change (sd 0 to 77) (g)[a]							
	181 0 ‡‡ ± 7 1 §§§ N=30	189 5 ± 9 3 N=30	182 0 ± 8 3 N=30	180 4 ± 7 3 N=30	189 4 ± 7 1 N=30	179 2 ± 9.8 N=30	148 9 * ± 6.8 N=30
Body Weight Change (sd 77 to 84) (g)[a,b]							
	8 0 ± 1 4 N=15	8.6 ± 1 8 N=15	4 5 ± 1 5 N=15	6 4 ± 2 1 N=15	5 5 ± 1 8 N=15	8 4 ± 1.3 N=15	4.6 ± 0.9 N=15

[a]Reported as the mean ± S E M , sd=study day with study day 0 being the first day of the post-wean holding period
[b]Females were scheduled for sacrifice over a two week period (cohort 1 the first week and cohort 2 the second week), therefore this endpoint includes only those females that were scheduled for sacrifice during the second week Statistical analyses were not performed on these endpoints since not all females were represented
#Bartlett's test for homogeneity of variances was significant ($p<0.001$) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05; ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test
§p<0 05, Test for Linear Trend.
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05; Dunnett's Test
***p<0 001, Dunnett's Test.
¶¶¶p<0 001, Kruskal-Wallis Test
¥p<0 05, Jonckheere's Test
¥¥¥p<0 001; Jonckheere's Test
¤¤¤p<0 001; Mann-Whitney U Test

Table 103 Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 1 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0.015	0 300	4 500	75 000	750.000	7500.000
No Males at Terminal Sacrifice	30	30	29[a]	30	30	30	30
Sacrifice Body Weight (g)[b]	501.31 ‡‡‡ ± 7 50 §§§ N=30	505.53 ± 9 19 N=30	493.46 ± 8 67 N=29	506 20 ± 7 77 N=30	517 90 ± 9 81 N=30	476 05 ± 8.21 N=30	368.92 *** ± 5 02 N=30
Liver Weight (g)[b]	21 4793 ‡‡‡ ± 0 5375 §§§ N=30	21.6156 ± 0.6083 N=30	20 7505 ± 0 5513 N=29	22 1476 ± 0 6540 N=30	21 7848 ± 0 5434 N=30	18.6064 ** ± 0 4756 N=30	15 0312 *** ± 0 3122 N=30
Paired Kidney Weight (g)[b]	3 9372 ‡‡‡ ± 0.0612 §§§ N=30	4.0018 ± 0.0631 N=30	3 9624 ± 0.0802 N=29	4 0242 ± 0 0911 N=30	4 0645 ± 0 0726 N=30	3 7561 ± 0.0677 N=30	3 3731 *** ± 0 0466 N=30
Paired Adrenal Weight (g)[b]	0 0644 ‡‡‡ ± 0 0020 §§§ N=29[c]	0 0688 ± 0 0020 N=30	0.0671 ± 0 0027 N=29	0 0691 ± 0 0021 N=30	0 0717 ± 0 0028 N=29[c]	0.0614 ± 0 0017 N=30	0 0571 ± 0 0014 N=30
Spleen Weight (g)[b]	0 8959 ‡‡‡ ± 0 0218 §§§ N=29[d]	0 8662 ± 0 0216 N=30	0.8747 ± 0 0239 N=29	0 9138 ± 0 0272 N=30	0 8236 ± 0.0216 N=29[d]	0 8315 ± 0 0237 N=30	0 6992 *** ± 0 0236 N=30
Brain Weight (g)[b]	2 0881 ‡‡‡ ± 0 0175 §§§ N=30	2 0824 ± 0 0213 N=30	2 0793 ± 0 0234 N=29	2.0793 ± 0.0211 N=30	2 0808 ± 0 0166 N=30	2.0825 ± 0 0136 N=30	1.9408 *** ± 0 0155 N=30

(continued)

Table 103 Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 2 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500.000
Pituitary Weight (g)[b]							
	0 0154 ‡‡‡ ± 0.0004 §§§ N=29[e]	0 0164 ± 0 0003 N=28[e]	0.0151 ± 0 0004 N=29	0 0158 ± 0 0004 N=29[e]	0.0158 ± 0.0003 N=29[e]	0 0154 ± 0.0003 N=29[e]	0.0135 *** ± 0 0003 N=30
Paired Testes Weight (g)[b]							
	3 6540 ‡‡‡ ± 0 0445 §§§ N=29[f]	3 4364 * ± 0 0823 N=30	3.3498 ** ± 0 0427 N=29	3 4998 ± 0 0581 N=30	3 4640 ± 0 0568 N=30	3 3037 *** ± 0.0492 N=30	3 1861 *** ± 0 0667 N=30
Paired Epididymis Weight (g)[b]							
	1 3382 ‡‡‡ ± 0 0190 §§§ N=30	1.2929 ± 0 0271 N=30	1 2879 ± 0 0188 N=29	1 3154 ± 0 0236 N=30	1 2769 ± 0 0253 N=30	1.2561 * ± 0.0227 N=30	1.1995 *** ± 0.0168 N=30
Prostate Weight (g)[b]							
	0 5550 ‡‡‡ ± 0 0238 §§§ N=30	0 5417 ± 0.0202 N=30	0 5952 ± 0 0259 N=29	0 5941 ± 0 0278 N=30	0 6199 ± 0.0240 N=30	0 5612 ± 0 0259 N=30	0 4167 *** ± 0.0159 N=30
Seminal Vesicles with Coagulating Gland Weight (g)[b]							
	1.7942 ‡‡‡ ± 0.0639 §§§ N=30	1 8491 ± 0 0547 N=30	1 8211 ± 0 0574 N=29	1 9325 ± 0 0586 N=30	1 8714 ± 0 0478 N=30	1 6990 ± 0 0529 N=30	1.4328 *** ± 0.0450 N=30
Preputial Gland Weight (g)[b]							
	0 1923 ± 0 0119 § N=29[g]	0 1934 ± 0 0135 N=30	0 2036 ± 0.0106 N=29	0.2262 ± 0 0144 N=30	0 2047 ± 0 0145 N=30	0 1949 ± 0 0101 N=30	0.1711 ± 0 0096 N=30

(continued)

Table 103 Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 3 of 6)

	Bisphenol A (ppm in the feed)						
	0.000	0 015	0 300	4 500	75.000	750 000	7500 000
Relative Liver Weight (% sacrifice weight)[b]							
	4 2802 ‡‡ ± 0.0770 N=30	4 2674 ± 0 0805 N=30	4 2045 ± 0 0820 N=29	4.3683 ± 0 1042 N=30	4.2047 ± 0 0638 N=30	3 9043 ** ± 0.0644 N=30	4 0763 ± 0 0701 N=30
Relative Paired Kidney Weight (% sacrifice weight)[b]							
	0 7877 ‡‡‡ ± 0.0113 §§§ N=30	0 7954 ± 0 0129 N=30	0 8043 ± 0 0115 N=29	0 7948 ± 0 0126 N=30	0 7876 ± 0 0115 N=30	0 7913 ± 0.0118 N=30	0 9156 *** ± 0 0094 N=30
Relative Paired Adrenal Weight (% sacrifice weight)[b]							
	0 0130 ‡‡ ± 0.0004 §§§ N=29[c]	0 0137 ± 0 0005 N=30	0.0136 ± 0 0005 N=29	0.0137 ± 0 0004 N=30	0 0139 ± 0 0005 N=29[c]	0.0130 ± 0.0004 N=30	0 0155 *** ± 0 0004 N=30
Relative Spleen Weight (% sacrifice weight)[b]							
	0 1805 ‡‡‡ ± 0.0053 §§ N=29[d]	0 1720 ± 0 0039 N=30	0 1773 ± 0 0037 N=29	0 1800 ± 0.0040 N=30	0 1593 ** ± 0 0032 N=29[d]	0 1748 ± 0 0043 N=30	0 1890 ± 0.0053 N=30
Relative Brain Weight (% sacrifice weight)[b]							
	0 4190 ‡‡‡ ± 0.0067 §§§ N=30	0 4156 ± 0 0083 N=30	0 4247 ± 0.0084 N=29	0 4126 ± 0 0056 N=30	0 4054 ± 0 0073 N=30	0.4407 ± 0 0071 N=30	0.5287 *** ± 0 0079 N=30
Relative Pituitary Weight (% sacrifice weight)[b]							
	0.0031 ‡‡‡ ± 0 0001 §§§ N=29[e]	0 0033 ± 0 0001 N=28[e]	0 0031 ± 0.0001 N=29	0 0031 ± 0 0001 N=29[e]	0 0031 ± 0 0001 N=29[e]	0 0033 ± 0.0001 N=29[e]	0 0037 *** ± 0 0001 N=30

(continued)

Table 103. Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 4 of 6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75 000	750.000	7500.000
Relative Paired Testes Weight (% sacrifice weight)[b]							
	0 7323 ‡‡‡ ± 0 0144 §§§ N=29[f]	0 6857 ± 0 0209 N=30	0 6842 ± 0 0139 N=29	0 6951 ± 0 0143 N=30	0 6739 ± 0 0140 N=30	0 6989 ± 0 0145 N=30	0 8669 *** ± 0 0195 N=30
Relative Paired Epididymis Weight (% sacrifice weight)[b]							
	0 2689 ‡‡‡ ± 0 0061 §§§ N=30	0 2580 ± 0.0071 N=30	0.2629 ± 0 0054 N=29	0 2615 ± 0.0060 N=30	0 2477 ± 0 0048 N=30	0.2657 ± 0 0060 N=30	0 3264 *** ± 0.0055 N=30
Relative Prostate Weight (% sacrifice weight)[b]							
	0.1112 ± 0.0049 N=30	0.1082 ± 0 0044 N=30	0.1207 ± 0 0051 N=29	0 1178 ± 0 0057 N=30	0.1201 ± 0 0047 N=30	0 1181 ± 0 0052 N=30	0.1134 ± 0.0045 N=30
Relative Seminal Vesicles with Coagulating Gland Weight (% sacrifice weight)[b]							
	0 3573 ± 0.0115 N=30	0 3669 ± 0 0103 N=30	0 3692 ± 0 0100 N=29	0.3832 ± 0.0118 N=30	0.3627 ± 0 0085 N=30	0.3574 ± 0 0104 N=30	0.3891 ± 0.0122 N=30
Relative Preputial Gland Weight (% sacrifice weight)[b]							
	0 0385 ± 0 0024 § N=29[g]	0 0386 ± 0.0027 N=30	0 0412 ± 0 0020 N=29	0 0446 ± 0.0028 N=30	0 0397 ± 0 0028 N=30	0 0414 ± 0 0023 N=30	0 0464 ± 0 0026 N=30
Percent Motile Sperm[b]							
	72.4 ± 1.8 N=30	69 8 ± 3 0 N=30	70 1 ± 2 0 N=29	73.4 ± 1 9 N=30	68 2 ± 3 0 N=30	68.1 ± 2 0 N=30	74.6 ± 1 8 N=30

(continued)

Table 103 Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation—(page-5-of-6)

	Bisphenol A (ppm in the feed)						
	0 000	0 015	0 300	4 500	75.000	750 000	7500.000
Percent Progressively Motile Sperm[b]							
	63 9 ± 1 8 N=30	62 3 ± 2 9 N=30	62 5 ± 2 0 N=29	63 5 ± 1 9 N=30	57 7 ± 3 1 N=30	59 0 ± 2 0 N=30	65 4 ± 2.1 N=30
Epididymal Sperm Concentration (mil/g)[b]							
	899 10 ± 28 55 N=30	897.19 ± 38 31 N=30	911 87 ± 35 47 N=29	923 84 ± 29 24 N=30	860 96 ± 31 93 N=30	929 36 ± 31 70 N=30	867 95 ± 27 80 N=30
Spermatid Head Concentration (mil/g)[b]							
	88.34 ± 4 23 N=30	84.27 ± 3 87 N=30	83 91 ± 2 37 N=29	84 28 ± 3 20 N=30	82 18 ± 2 96 N=30	88 79 ± 4 43 N=30	80 94 ± 3 25 N=30
Daily Sperm Production per Testis[b]							
	34 84 ‡ ± 1 71 § N=30	30 27 ± 1.23 N=30	30 66 ± 0 94 N=29	32 07 ± 1 35 N=30	30 63 ± 1 35 N=30	31 87 ± 1 63 N=30	28 21 ** ± 1 20 N=30
Efficiency of Daily Sperm Production[b]							
	19 16 ± 0 92 N=30	18.28 ± 0 84 N=30	18 20 ± 0 51 N=29	18 28 ± 0 69 N=30	17 83 ± 0 64 N=30	19 26 ± 0 96 N=30	17 56 ± 0.71 N=30
Percent Abnormal Sperm[b]							
#	1 75 ± 0 16 N=30	5 14 ± 3 23 N=30	1 93 ± 0 20 N=29	2.29 ± 0 28 N=30	8 33 ± 4 20 N=30	1.70 ± 0.16 N=30	2 03 ± 0 36 N=30

(continued)

Table 103 Summary and Statistical Analysis of the F_3 Male Organ Weights and Relative Organ Weights at Scheduled Sacrifice and Sperm Evaluation (page 6 of 6)

[a]Male 3095 was euthanized moribund on study day -5
[b]Reported as the mean ± S E M
[c]Decrease in N is due to the paired adrenal weight for one male being unrealistic and therefore not included
[d]Decrease in N is due to the spleen weight for one male being unrealistic and therefore not included
[e]Decrease in N is due to the pituitary inadvertently not being saved for one or more males
[f]Decrease in N is due to the paired testes weight for one male being unrealistic and therefore not included
[g]Decrease in N is due to the preputial gland weight for one male inadvertently not being recorded.
#Bartlett's test for homogeneity of variances was significant (p<0 001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05, ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0.001, ANOVA Test
§p<0 05, Test for Linear Trend
§§p<0 01, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
*p<0 05, Dunnett's Test
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test

Table 105 Summary and Statistical Analysis of the F_3 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 1 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0.3	4.5	75	750	7500
No Females at Scheduled Sacrifice	30	30	30	30	30	30	30
Sacrifice Body Weight (g)[a]							
	290.4 ‡‡‡ ± 3 9 §§§ N=30	302 9 ± 4 6 N=30	286 9 ± 6.6 N=29[b]	293 5 ± 5 6 N=30	295 4 ± 3 5 N=30	282 9 ± 5.9 N=29[b]	233.6 *** ± 4 9 N=30
Liver Weight (g)[a]							
	11.5084 ‡‡‡ ± 0 2118 §§§ N=30	11 9200 ± 0 2708 N=30	11 2958 ± 0 2919 N=30	12 1090 ± 0 3600 N=29[c]	11 5538 ± 0 2364 N=30	10 9952 ± 0 2832 N=30	9.5361 *** ± 0.2068 N=30
Paired Kidney Weight (g)[a]							
	2 3539 ‡‡‡ ± 0 0413 §§§ N=30	2 3757 ± 0 0429 N=30	2 2940 ± 0 0412 N=30	2 3319 ± 0 0468 N=30	2.3888 ± 0 0388 N=30	2 3145 ± 0 0408 N=30	1.9280 *** ± 0.0351 N=30
Paired Adrenal Weight (g)[a]							
	0.0719 ‡‡‡ ± 0.0022 §§§ N=29[c]	0.0728 ± 0 0028 N=29[d]	0.0727 ± 0.0024 N=29[d]	0 0751 ± 0.0026 N=29[d]	0.0759 ± 0 0029 N=30	0 0732 ± 0 0026 N=30	0 0581 *** ± 0 0015 N=30
Spleen Weight (g)[a]							
#	0 5434 ¶¶ ± 0 0148 N=30	0 5421 ± 0.0145 N=30	0 5279 ± 0 0142 N=30	0.6122 ± 0 0713 N=28[c,e]	0 5115 ± 0 0129 N=30	0 5701 ± 0 0182 N=30	0 4896 ¤ ± 0 0141 N=30
Brain Weight (g)[a]							
	1.9308 ‡ ± 0 0227 §§§ N=30	1.9385 ± 0 0293 N=30	1 9639 ± 0 0262 N=30	1 9264 ± 0.0239 N=30	1 9486 ± 0 0242 N=29[c]	1 9346 ± 0.0188 N=30	1 8527 ± 0.0205 N=30

(continued)

Table 105 Summary and Statistical Analysis of the F_3 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 2 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Pituitary Weight (g)[a]							
	0 0185 ‡‡‡ ± 0 0007 §§§ N=30	0 0201 ± 0 0007 N=29[f]	0 0187 ± 0 0006 N=30	0 0191 ± 0 0008 N=29[f]	0 0191 ± 0 0007 N=30	0 0188 ± 0 0006 N=29[g]	0.0154 ** ± 0 0003 N=30
Paired Ovary Weight (g)[a]							
	0 1402 ‡‡ ± 0 0050 §§§ N=30	0 1298 ± 0 0043 N=29[h]	0 1351 ± 0 0049 N=29[h]	0 1318 ± 0 0049 N=29[h]	0 1416 ± 0.0051 N=29[h]	0.1398 ± 0.0041 N=30	0.1178 ** ± 0.0036 N=30
Uterus Weight (g)[a]							
	0.6651 ± 0 0421 N=30	0 6568 ± 0 0299 N=30	0 7113 ± 0.0393 N=30	0 6757 ± 0 0272 N=29[i]	0 6837 ± 0.0304 N=29[i]	0.6866 ± 0.0331 N=30	0.6218 ± 0 0348 N=30
Relative Liver Weight (% sacrifice weight)[a]							
	3 9645 ‡ ± 0.0542 N=30	3 9328 ± 0 0621 N=30	3 9279 ± 0.0589 N=29[b]	4 1245 ± 0.0639 N=29[c]	3 9079 ± 0 0596 N=30	3 8629 ± 0.0545 N=29[b]	4.0887 ± 0.0511 N=30
Relative Paired Kidney Weight (% sacrifice weight)[a]							
	0.8112 ± 0 0109 § N=30	0.7862 ± 0 0126 N=30	0 8008 ± 0 0122 N=29[b]	0.7961 ± 0 0106 N=30	0.8101 ± 0 0128 N=30	0 8190 ± 0 0100 N=29[b]	0.8281 ± 0 0106 N=30
Relative Paired Adrenal Weight (% sacrifice weight)[a]							
	0 0250 ± 0 0009 N=29[c]	0 0243 ± 0 0010 N=29[d]	0 0256 ± 0.0010 N=28[b,d]	0 0257 ± 0 0009 N=29[d]	0 0258 ± 0.0010 N=30	0 0260 ± 0 0011 N=29[b]	0.0251 ± 0 0007 N=30

(continued)

Table 105 Summary and Statıstıcal Analysıs of the F_3 Female Organ Weıghts and Relatıve Organ Weıghts at Scheduled Sacrıfice, Paıred Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 3 of 5)

	Bısphenol A (ppm ın the feed)						
	0	0 015	0.3	4 5	75	750	7500
Relatıve Spleen Weıght (% sacrıfice weight)[a]							
#	0 1877 ¶¶¶ ± 0 0051 ¥¥¥ N=30	0 1790 ± 0 0040 N=30	0 1838 ± 0.0044 N=29[b]	0 2104 ± 0.0223 N=28[c,e]	0 1739 ± 0 0049 N=30	0 1986 ± 0.0050 N=29[b]	0.2098 ¤¤ ± 0.0048 N=30
Relatıve Braın Weıght (% sacrıfice weıght)[a]							
	0 6671 ‡‡‡ ± 0 0091 §§§ N=30	0 6437 ± 0 0126 N=30	0 6912 ± 0 0163 N=29[b]	0 6616 ± 0 0125 N=30	0 6593 ± 0 0092 N=29[c]	0 6924 ± 0 0143 N=29[b]	0 8013 *** ± 0.0159 N=30
Relatıve Pıtuıtary Weight (% sacrıfice weight)[a]							
	0 0064 ± 0 0002 N=30	0 0067 ± 0 0002 N=29[f]	0.0065 ± 0.0002 N=29[b]	0 0065 ± 0.0002 N=29[f]	0 0065 ± 0.0002 N=30	0 0067 ± 0 0002 N=28[b,g]	0.0066 ± 0.0002 N=30
Relatıve Paıred Ovary Weight (% sacrifice weıght)[a]							
	0.0484 ‡ ± 0 0017 § N=30	0 0433 ± 0.0016 N=29[h]	0 0467 ± 0.0016 N=28[b,h]	0 0457 ± 0.0019 N=29[h]	0 0479 ± 0.0017 N=29[h]	0 0488 ± 0 0010 N=29[b]	0.0509 ± 0.0017 N=30
Relatıve Uterus Weıght (% sacnfice weıght)[a]							
	0 2290 ± 0 0144 § N=30	0 2196 ± 0 0122 N=30	0 2524 ± 0 0156 N=29[b]	0.2339 ± 0.0110 N=29[i]	0.2300 ± 0 0094 N=29[i]	0 2473 ± 0.0130 N=29[b]	0 2687 ± 0.0152 N=30

(continued)

Table 105 Summary and Statistical Analysis of the F_3 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 4 of 5)

	Bisphenol A (ppm in the feed)						
	0	0 015	0 3	4 5	75	750	7500
Paired Ovarian Follicle Count[a,j]							
	384 6 ± 55 7 N=10						355 4 ± 38 3 N=10
VAGINAL CYTOLOGY EVALUATION AT NECROPSY[k]							
No Females Evaluated	30	30	30	29[l]	30	30	30
No in Proestrus	3	2	4	3	5	9	5
% in Proestrus	10 34 Ψ	6 67	13.33	10 34	16 67	31 03	16 67
No in Estrus	9	12	12	13	15	4	10
% in Estrus	31.03	40 00	40 00	44 83	50 00	13 79	33.33
No in Metestrus	2	1	4	3	2	3	3
% in Metestrus	6 90	3.33	13 33	10 34	6 67	10.34	10.00
No in Diestrus	15	15	10	10	8	13	12
% in Diestrus	51 72	50 00	33 33	34 48	26.67	44 83	40.00
No Stage Not Determined	1	0	0	0	0	1	0
No No Cells Present	0	0	0	0	0	0	0

(continued)

Table 105 Summary and Statistical Analysis of the F_3 Female Organ Weights and Relative Organ Weights at Scheduled Sacrifice, Paired Ovarian Follicle Counts and Vaginal Cytology at Necropsy (page 5 of 5)

[a]Reported as the mean ± S E M
[b]Decrease in N is due to the sacrifice weight for one female inadvertently not being recorded
[c]Decrease in N is due to one weight being a statistical outlier and therefore it was removed.
[d]Decrease in N is due to the paired adrenal weight for one female being unrealistic and therefore not included
[e]Decrease in N is due to the spleen weight for one female being unrealistic and therefore not included
[f]Decrease in N is due to the pituitary inadvertently not being saved for one female
[g]Decrease in N is due to the pituitary weight for one female being unrealistic and therefore not included
[h]Decrease in N is due to the paired ovary weight for one female being unrealistic and therefore not included
[i]Decrease in N is due to the uterus weight for one female being unrealistic and therefore not included
[j]Ovarian follicle counts were done for 10 control females and 10 females in the 7500 000 ppm Bisphenol A dose group
[k]For prsentation 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
[l]Vaginal smear for one or more females inadvertently not done.
#Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed
‡p<0 05; ANOVA Test
‡‡p<0 01, ANOVA Test
‡‡‡p<0 001, ANOVA Test.
§p<0 05, Test for Linear Trend
§§§p<0 001, Test for Linear Trend
**p<0 01, Dunnett's Test
***p<0 001, Dunnett's Test
¶p<0 05, Kruskal-Wallis Test.
¶¶p<0 01, Kruskal-Wallis Test
¶¶¶p<0 001, Kruskal-Wallis Test
¥¥¥p<0 001, Jonckheere's Test
¤p<0 05, Mann-Whitney U Test
¤¤p<0 01, Mann-Whitney U Test
Ψp<0 05, Cochran-Armitage Test

TOXICOLOGICAL SCIENCES 68, 121–146 (2002)

Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats

R. W. Tyl,*[1] C. B. Myers,* M. C. Marr,* B. F. Thomas,* A. R. Keimowitz,* D. R. Brine,* M. M. Veselica,* P. A. Fail,* T. Y. Chang,* J. C. Seely,† R. L. Joiner,‡ J. H. Butala,§ S. S. Dimond,‡ S. Z. Cagen,¶ R. N. Shiotsuka,‖ G. D. Stropp,‖‖ and J. M. Waechter‖‖‖

*RTI, Research Triangle Park, North Carolina; †EPL, Inc., Research Triangle Park, North Carolina; ‡GE Plastics, Pittsfield, Massachusetts; §Aristech Chemical Corp., Pittsburgh, Pennsylvania; ¶Shell Chemical Co., Houston, Texas; ‖Bayer Corp., Stilwell, Kansas; ‖‖Bayer AG, Wuppertal, Germany; and ‖‖‖The Dow Chemical Co., Midland, Michigan

Received March 20, 2001; accepted February 11, 2002

Bisphenol A (BPA) was evaluated at concentrations of 0, 0.015, 0.3, 4.5, 75, 750, and 7500 ppm (~ 0.001, 0.02, 0.3, 5, 50, and 500 mg/kg/day of BPA) administered in the diet *ad libitum* to 30 CD® Sprague-Dawley rats/sex/dose for 3 offspring generations, 1 litter/generation, through F3 adults. Adult systemic toxicity at 750 and 7500 ppm in all generations included: reduced body weights and body weight gains, reduced absolute and increased relative weanling and adult organ weights (liver, kidneys, adrenals, spleen, pituitary, and brain), and female slight/mild renal and hepatic pathology at 7500 ppm. Reproductive organ histopathology and function were unaffected. Ovarian weights as well as total pups and live pups/litter on postnatal day (PND) 0 were decreased at 7500 ppm, which exceeded the adult maximum tolerated dose (MTD). Mating, fertility, gestational indices, ovarian primordial follicle counts; estrous cyclicity; precoital interval; gestational length, offspring sex ratios, postnatal survival, nipple/areolae retention in preweanling males, epididymal sperm number, motility, morphology; daily sperm production (DSP), and efficiency of DSP were all unaffected. At 7500 ppm, vaginal patency (VP) and preputial separation (PPS) were delayed in F1, F2, and F3 offspring, associated with reduced body weights. Anogenital distance (AGD) on PND 0 was unaffected for F2 and F3 males and F3 females (F2 female AGD was increased at some doses, not at 7500 ppm, and was considered not biologically or toxicologically relevant). Adult systemic no observed adverse effect level (NOAEL) = 75 ppm (5 mg/kg/day); reproductive and postnatal NOAELs = 750 ppm (50 mg/kg/day). There were no treatment-related effects in the low-dose region (0.001–5 mg/kg/day) on any parameters and no evidence of nonmonotonic dose-response curves across generations for either sex. BPA should not be considered a selective reproductive toxicant, based on the results of this study.

Key Words: Bisphenol A; CAS No. 80-05-7; dietary administration, systemic toxicity, reproductive toxicity, postnatal toxicity; OPPTS 837.3800 guidelines.

Bisphenol A (BPA) is a high production volume chemical used principally as a monomer in the manufacture of numerous chemical products, including polycarbonate plastics and epoxy resins. Industrial exposure during the manufacture and use of the monomer is variable, depending on the use and duration of exposure. Consumer exposure to BPA may be possible from migration of BPA from dental sealants or from polycarbonate or epoxy-lined food and drink containers. Although it had been known for decades that BPA has weak estrogen-like activity *in vivo* by sc injection (Dodds and Lawson, 1936), there has been recent, renewed interest in its potential for estrogen-like activity. Krishnan *et al.* (1993) discovered that BPA leaching from polycarbonate flasks during autoclaving induced an estrogen-like response in yeast cultures. Gaido *et al.* (1997) confirmed its estrogen-like activity *in vitro*, calculating BPA as approximately 15,000-fold less potent than 17β-estradiol (E2). Kuiper *et al.* (1997) demonstrated that BPA could interact with both the α- and β-estrogen receptors. Kuiper *et al.* (1998) also showed that the *in vitro* binding affinity of BPA was approximately 10,000-fold less potent than that of E2 and 20,000-fold less potent than diethylstilbestrol (DES) for both ERα and ERβ. Maruyama *et al.* (1999) also reported BPA to be 10,000-fold less potent than E2 *in vitro* using an E2 responsive rat pituitary cell line.

In vivo, Milligan *et al.* (1998) showed BPA to be 10,000-fold less potent in producing a uterotrophic effect than estradiol following sc injections into ovariectomized mice. Ashby and Tinwell (1998), Jekat *et al.* (2000), Kim *et al.* (2001), Laws *et al.* (2000), Matthews *et al.* (2001), and Yamasaki *et al.* (2000) also reported uterotrophic effects in rats following high oral and/or sc dosing, and Goloubkova *et al.* (2000) reported stimulatory effects on the growth of the pituitary gland following high sc doses of BPA.

Research conducted in the 1970s and 1980s, using 1-generation (CD rats) or 2-generation continuous breeding (CD-1 mice) designs, indicated that BPA was not a selective reproductive toxicant with high dietary BPA concentrations (Mor-

[1] To whom correspondence should be addressed at RTI, 245 MCB/HLB, P.O. Box 12194, 3040 Cornwallis Road, Research Triangle Park, NC 27709-2194. Fax: (919) 541-5956. E-mail: rwt@rti.org

rissey *et al* 1989, Wazeter and Goldenthal, 1984a,b) Standard Segment II developmental toxicity studies in CD rats and CD-1 mice administered BPA at high doses by gavage on gestational day (GD) 6–15 indicated that BPA was not a selective developmental toxicant (Morrissey *et al*, 1987) More recently, Liaw *et al* (1998) showed that exposure of pregnant SD (Sprague-Dawley) rats to BPA in drinking water from GD 2 through lactation (until PND 21) at 0, 0.005, 0 05, 0.5, 5, or 50 mg/l (ppm) and DES at 0 05 mg/l (ppm) did not affect the age or body weight at acquisition of VP and had no significant effects on reproductive organ development DES accelerated acquisition of VP (with reduced body weights)

In contrast to the "high" dose studies above, oral administration (presentation to the dam's buccal cavity) of BPA at 2 and 20 μg/kg/day in corn oil to pregnant CF-1 mice on GD 11–17 was reported to increase prostate gland weight at both doses and decrease DSP per gram testis (efficiency of DSP) at 20 μg kg/day in offspring males (Nagel *et al*, 1997, vom Saal *et al*, 1998) However, these reported low-dose effects of BPA could not be reproduced in more robust studies designed with larger numbers of animals and the same (Ashby *et al*, 1999) and additional lower and higher doses (Cagen *et al*, 1999a), and the NTP Low-Dose Peer Review's Statistical Subpanel could not confirm the statistical significance of the decreased DSP per gram testis at 20 μg/kg/day (NTP, 2001)

In another study examining low-dose exposure, adult male offspring of female Wistar rats exposed to 1 ppm BPA (corresponding to approximately 0 1–0 4 mg/kg/day) in their drinking water for 8 to 9 weeks (during prebreed, mating, gestation, and lactation) were reported to exhibit significantly reduced testes weights (Sharpe *et al*, 1995) The results of this study were brought into question when the original authors could not reproduce their initial findings or other studies that had produced the same results in different chemicals (Sharpe *et al*, 1998) The results of the initial study with BPA could also not be reproduced in another study using the same exposure route, timing, and strain of rat, but with a larger number of dose groups, more animals per dose, and more reproductive parameters (Cagen *et al*, 1999b) The studies previously reported as positive usually had smaller numbers of animals, fewer doses, and/or parenteral routes of administration Therefore, the present study was designed and performed to definitively evaluate the concerns for possible low-dose effects, for possible nonmonotonic ("inverted-u") dose-response curves, and for possible effects of exposure to BPA by a relevant route of administration during sensitive life stages (pre- and early postnatal), as well as postweaning peripubertal maturational stages, over 3 generations of offspring using an internationally accepted reproductive toxicity protocol under Good Laboratory Practice (GLP) regulations (U S EPA, 1989)

Specifically, this study evaluated exposure of CD® (SD) rats (30/sex/group) to BPA administered in the diet *ad libitum* at 0, 0 015, 0 3, 4 5, 75, 750, and 7500 ppm (resulting in BPA intakes of ~ 0 001, 0 02, 0 3, 5, 50, and 500 mg/kg/day) for 3 generations, 1 litter per generation, using the U S EPA OPPTS test guidelines (U S EPA OPPTS 837.3800, 1998) Additional assessments beyond the guideline requirements included a third offspring generation, 1 control and 6 treatment groups, examination for retained nipples and areolae in male F1, F2, and F3 preweanlings, and retention of F3 offspring until adulthood with continuing exposure, with histopathologic and andrological assessments at their termination

MATERIALS AND METHODS

Test material and dietary formulations. BPA (4,4'-isopropylidene-2'-diphenol, CAS No 80-05-7) was obtained in one shipment and lot number from Acros Organics NV (Fairlawn, NJ) as a 99 5% pure white crystalline solid and purity was reconfirmed throughout the study

The basic diet was Purina Certified Rodent Chow® (No 5002, PMI Feeds, Inc , St Louis, MO) Dosed diets were formulated by dissolving BPA in a fixed volume of acetone as separate stock solutions, 1 for each dietary dose Each BPA-acetone stock solution was added to a premix feed aliquot After evaporating the acetone, each premix was blended with additional feed to make the prescribed concentrations for each of the 17 formulation dates Control diets were formulated as described above

Stability of formulations at 15 ppb and 7500 and 10,000 ppm was confirmed at approximately -20°C for 50 days, and at room temperature in open containers to simulate cageside conditions for at least 9 days Homogeneity was also confirmed by assaying 1 sample each at 15 ppb and 7500 and 10,000 ppm in triplicate from 3 locations within the blender Aliquots from all dosed feed preparations were analyzed for BPA concentration, and the diet was used only if within the acceptable range (± 15% of the nominal) All analyses of the feed were performed using negative ion CI (chemical ionization) gas chromatography-mass spectrometry (GC-MS) analysis The estimated limit of detection was 0 0008–0 0018 ppm

Formulated diets were stored at –20°C for up to 50 days in sealed containers Feed was changed at least every 7 days

Animals and husbandry. The SD rat is recommended for use in reproductive and developmental toxicity testing by worldwide regulatory agencies such as the U S EPA, OECD, and Japanese MAFF It was also chosen for this study because of the extensive historical database with this strain at RTI Two hundred forty virgin female and male rats were ordered for the study Ten/sex were used as quality controls for assessment of viral antibody status within 1 day after receipt, 8/sex were used as sentinels for monitoring of health status of study animals (with 2/sex each evaluated for viral antibody titers at the necropsy of F0, F1, F2, and F3 adults), 12/sex were available to replace any animals inappropriate for use, and 210/sex went on study All viral antibody titer assessments for quality control and sentinel animals were negative

At the end of the approximately 1-week quarantine period, all animals were in good health and were randomly distributed into 7 strata by sex and body weight The rats within each stratum were then randomly assigned, 1 to each treatment group using a random number table, and uniquely identified by eartag and animal study numbers All selected weanling offspring were also identified by eartag and animal study numbers

The animals were individually housed in stainless-steel hanging cages upon arrival, during the acclimation period, and upon the initiation of the treatment period An automatic watering system was used for all animals during prebreed and for the males after mating during the holding period Mating pairs (1 male 1 female) and sperm/plug positive females, from GD 0 until weaning of their litters on PND 21, were housed in solid-bottom polypropylene cages (Laboratory Products, Rochelle Park, NJ), with Sani-Chip® cage bedding (P J Murphy Forest Products, Inc , Montville, NJ) with glass water bottles The caging, water bottles and sipper tubes, and storage containers for feed were made from materials that did not contain BPA to prevent any extraneous exposure of animals Temperature (64–79°F) 12-h light/dark cycle, and rel-

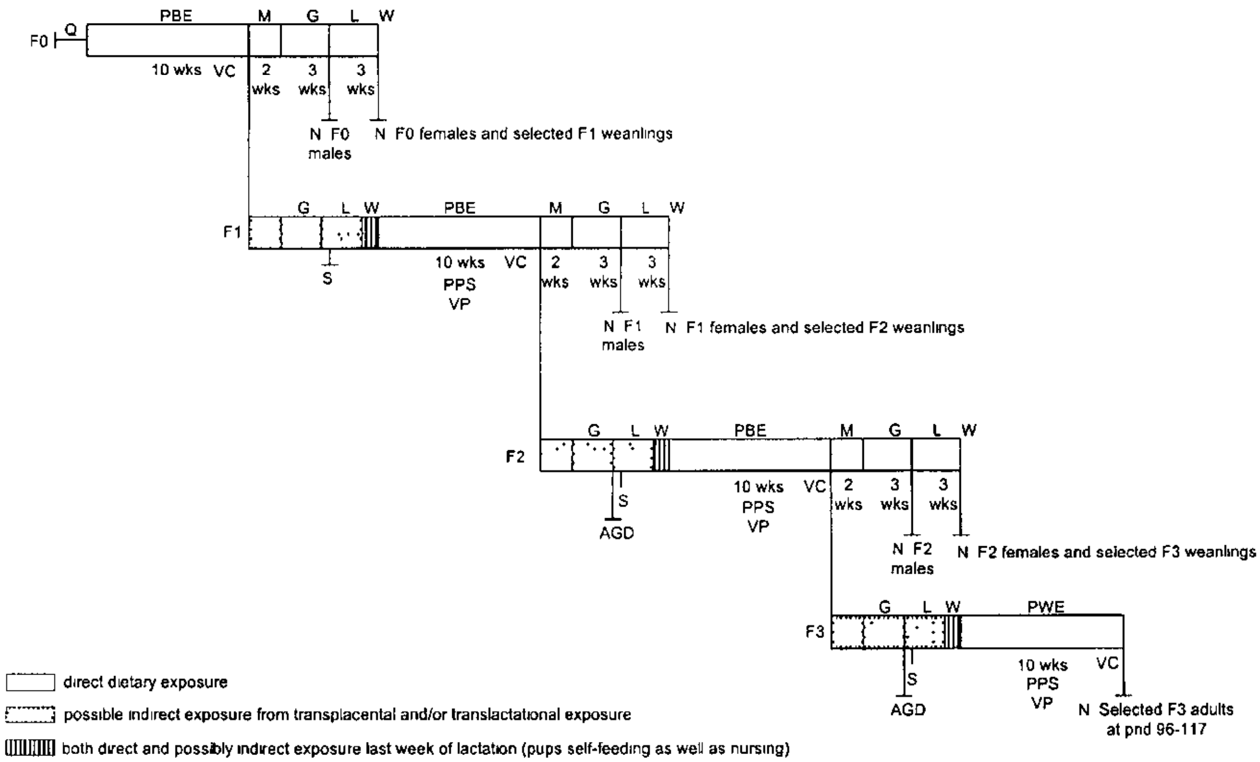

FIG 1 BPA 3-generation study design Q, quarantine (1 week), PBF, prebreed exposure (10 weeks), M, mating (2 weeks), G, gestation (3 weeks), L, lactation (3 weeks) N, necropsy AGD, anogenital distance on PND 0 for F2 and F3 offspring ("triggered" endpoint) VC, vaginal cytology (evaluated in females during last 3 weeks of prebreed/postwean period), VP vaginal patency evaluated in offspring females (PND 22–acquisition), S, standardize litters to 10 pups with equal sex ratio PND 4, PWE, postwean exposure 10 weeks F3 offspring (until PND 96-117), PPS preputial separation evaluated in offspring males (PND 35–acquisition), W, weaning (PND 21)

ative humidity (30–70%) in the animal rooms were continuously monitored, controlled, and automatically recorded

Purina Certified Ground Rodent Chow (No 5002, PMI Feeds, Inc, St Louis MO) was available *ad libitum*, 7 days per week, 24 hours per day, throughout the study The analyses of each feed batch for nutrient levels and possible contaminants were performed by the supplier The supplier reported total isoflavone content (as aglycone equivalents) of 309 2 µg/g feed (range 290 0–358 0 µg/g), of which genistein was 127 6 µg/g (113 0–139 0 µg/g) and daidzein was 131 3 µg/g (114 0 -167 0 µg/g) Total protein content was 20 1% For all feed batches, nutrient levels were at or above, and contaminant levels were below the certified levels, and therefore judged suitable for use Water was available *ad libitum* by an automatic watering system during the time the animals were in hanging cages, and by water bottles during the time the animals were in solid-bottom cages At all times, the regular analyses of the water showed that contaminants were below the maximum levels defined for drinking water

Study design. A graphic representation of the study design is presented in Figure 1 The study began with 30 males/group and 30 females/group (designated the F0 generation) to yield at least 20 pregnant females/group at or near term, and 7 groups (see Table 1) The target dietary concentrations (0, 0 015, 0 3, 4 5 75 750, and 7500 ppm) were selected to provide BPA intakes of approximately 0 001 0 02 0 3 5 50 and 500 mg/kg/day respectively to encompass the ranges of low oral BPA doses (0 002 and 0 02 mg/kg day) at which male mouse offspring prostate weights were reported to be significantly increased (Nagel *et al* 1997 vom Saal *et al* 1998), and of doses at which testis weight and efficiency of DSP were reported to be significantly reduced in rat offspring (Sharpe *et al*, 1995) The dietary concentrations were also chosen to provide an MTD that is expected to exceed the metabolic capability of the adult liver and to produce reductions in body weight or other indications of systemic toxicity The target dietary concentrations were based on the chosen BPA intakes in mg/kg/day for the female rats (Table 1)

Dietary BPA was available *ad libitum* to the F0 animals for a 10-week prebreed exposure period, during mating, during gestation, and females through lactation until weaning Body weights and feed consumption were recorded weekly, and clinical signs were recorded at least once daily Vaginal cytology was evaluated for the last 3 weeks of the prebreed period Animals were randomly mated within treatment groups for a 2-week period to produce the F1 generation All F0 males were necropsied after F1 delivery, with histopathologic evaluation of reproductive and other organs (all controls and 10 per dose, plus any gross lesions and reproductive tissues from unsuccessful breeders or animals suspected of reduced fertility) and andrological assessments (reproductive organ weights, epididymal sperm number, motility, and morphology, testicular homogenization-resistant spermatid head counts, DSP, and efficiency of DSP in all males in all groups, Robb *et al*, 1978, Sharpe *et al* 1995)

F1 litters were culled to 10 pups (with equal sex ratio, if possible) on PND 4, and F1 males were examined on PND 11–13 for retained areolae and/or nipples At weaning (PND 21), 30/sex/dose were then randomly selected as F1 parents of the F2 generation, and up to 3 remaining weanlings/sex/litter were randomly selected, necropsied, and selected organs weighed All F0 females were necropsied and selected organs were weighed The stage of estrus at necropsy and enumeration of ovarian primordial follicles (from step sections of both ovaries of ten females each at high dose and control) were determined,

TABLE 1
BPA Study Organization and Target Dietary Concentrations and Intakes

Group	No animals		Concentration (ppm)	Mean target BPA intake		
	Male	Female		Female	Male	Actual intake
1	30	30	0 0	0 00	0 00	0
2	30	30	0 015	0 001	0 0009	0 003–0 0007
3	30	30	0 3	0 02	0 018	0 062–0 015
4	30	30	4 5	0 30	0 27	0 73–0 22
5	30	30	75	5	4 5	15 4–4 1
6	30	30	750	50	45	167 2–37 6
7	30	30	7500	500	450	1823–434

Note Target and actual intakes are given in mg/kg/day Assumptions for females 300 g (0 3 kg) body weight and 20 g/day feed consumption Assumptions for males 500 g (0 5 kg) body weight and 30 g/day feed consumption For actual intake a range is provided since this was dependent on the age and sex of the animals and the phase of the study (e g , intake was highest for dams during the last week of lactation, confounded by pups self-feeding, and for offspring during the first week of the postwean/prebreed exposure period)

and histopathological examinations of reproductive and other selected organs (same as F0 males above) were performed

Selected F1 weanlings were administered BPA in the diet for the exposure period as described above for the F0 generation Acquisition of VP in F1 females and PPS in F1 males was determined during prebreed Vaginal cytology for estrous cyclicity was evaluated during the last 3 weeks of prebreed Since acquisition of puberty was delayed in F1 offspring at 7500 ppm measurement of AGD was performed on all F2 and F3 offspring at birth (PND 0) using an ocular micrometer and eyepiece grid (precision = 0 2 mm) At weaning of F2 litters, the same procedure as described above was used to select the F2 parents of the F3 generation All F1 males and females were necropsied, with histopathology as described above

Randomly selected F2 weanlings were administered BPA in the diet for the exposure period as described above for the F0 and F1 generations Acquisition of VP and PPS and evaluation of estrous cyclicity were performed as above for the F1 generation They were then mated as described above to generate F3 litters F2 parental animals were necropsied with histopathology as described above At weaning of F3 litters, up to 3 weanlings/sex/litter were randomly selected and necropsied, and 30/sex/dose were randomly selected and retained until adulthood (up to ~ 17 weeks), with exposures continuing, with acquisition of VP, PPS, and estrous cyclicity evaluated At necropsy of these retained adult F3 offspring, they were evaluated as described above for F0, F1, and F2 parental animals

Statistical analyses. The unit of comparison was the individual animal or the litter, as appropriate Data from the cohorts were combined for summarization and statistical analyses See Figure 2 for a graphical representation and reference citations of the decision trees employed for the statistical analyses Quantitative continuous data (e g parental and pup body weights, organ weights feed consumption, AGD etc) were compared among the 6 treatment groups and the vehicle control group For the litter-derived percentage data (e g periodic pup survival indices), the ANOVA was weighted according to litter size General Linear Models (GLM) analysis was used to determine the significance of the dose-response relationship and to determine whether significant dosage effects had occurred for selected measures A one-tailed test was used for all pairwise comparisons to the vehicle control group, except that a two-tailed test was used for parental and pup body weight and organ weight parameters, feed consumption, percent males per litter, and AGD per sex per litter (Figure 2A)

Nonparametric tests for continuous data were used to determine if significant differences were present among the groups or to identify significant dose-response trends (Figure 2A) Frequency data, such as reproductive indices (e g , mating and fertility indices), were analyzed for differences among treatment groups and for pairwise comparisons (Figure 2B)

For acquisition of developmental landmarks (e g , VP and PPS) and AGD, ANOVA and analysis of covariance (ANCOVA), with body weight (at birth, PND 0 for AGD, at acquisition of puberty and on study day [SD] 7 for females [VP] and SD 14 for males [PPS], see Discussion) as the covariate, were used for pairwise comparisons (Figure 2C) For correlated data (e g , body and organ weights at necropsy of weanlings, with more than 1 pup/sex/litter), SUDAAN® software was used for analysis of overall significance, presence of trend, and pairwise comparisons to the control group values (Figure 2D) For all statistical tests, the significance limit of 0 05 (one- or two-tailed) was used as the criterion for significance

A test for statistical outliers (SAS, 1990b) was performed on parental body weights and feed consumption (in g/day) and parental and weanling offspring organ weights at necropsy If examination of pertinent study data did not provide a plausible biologically sound reason (i e , a reason that could not be ruled out as being within the possible range for the organ or measurement being made) for inclusion of the data flagged as "outlier," the data were excluded from summarization and analysis and were designated as outliers

RESULTS

Parental Systemic Parameters 2

Body weights Adult systemic toxicity was evident for F0, F1, and F2 parental animals and F3 retained animals at 750 and 7500 ppm (50 and 500 mg/kg/day, respectively), including consistent and persistent reductions in body weights and weight gains in both sexes and in F0, F1, F2, and F3 generations Body weights for F1 males and females, during the prebreed and mating periods, are presented in Figure 3, these data are representative of all the generations evaluated Body weights during gestation and lactation were significantly reduced in F0, F1, and F2 females at 7500 ppm, and during gestation and lactation at 750 ppm for F0 and F2 females and for F1 females during lactation (Fig 4 for F1 females; these data are representative of all generations evaluated) Body weights at terminal sacrifice were significantly decreased in all generations at 7500 ppm, in F1 females at 750 ppm, and in F1 and F2 males at 750 ppm (Table 2) There were no toxicolog-

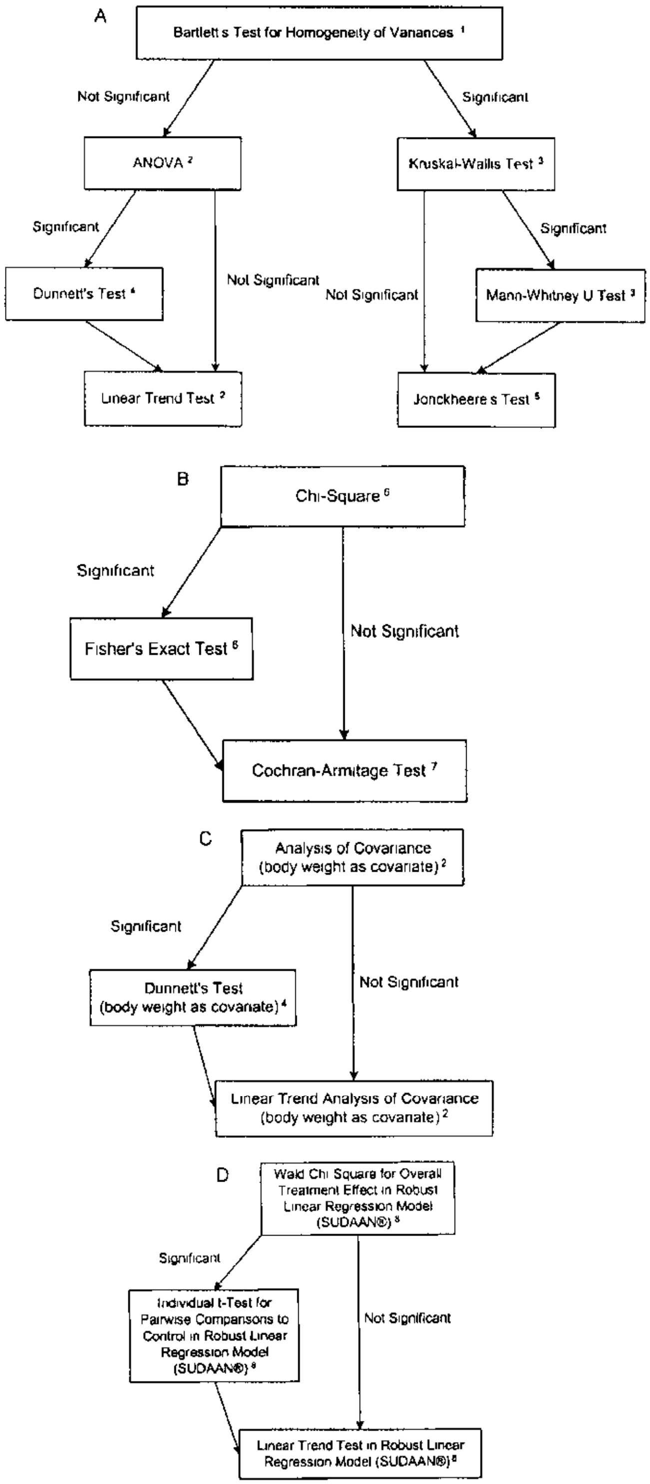

FIG 2 Decision trees for statistical analyses of study data (A) Quantitative continuous data, (B) frequency data, (C) analysis of covariance, and (D) correlated data [1]Winer (1962), [2]SAS Institute, Inc (1989a,b, 1990a,b,c, 1996, 1997) [3]Siegel (1956), [4]Dunnett (1955 1964), [5]Jonckheere (1954), [6]Snedecor and Cochran (1967), [7]Cochran (1954), Armitage (1955), Agresti (1990), [8]Shah *et al* (1997)

ically significant, consistent, or persistent effects on these parameters at 75 ppm (5 mg/kg/day) or below.

Feed consumption and BPA intake Feed consumption in g/day and g/kg/day was variable and showed no clear treatment-related effects (data not shown) The actual intake of BPA for both males and females throughout the study was 0, 0.0007–0.003, 0.015–0.062, 0.22–0.73, 4.1–15.4, 37.6–167.2, and 434–1823 mg/kg/day for the 0, 0.015, 0.3, 4.5, 75, 750, and 7500 ppm groups, respectively (Table 1) The BPA intake was highest in the prebreed (in both sexes, Fig 3) and lactation periods (in the females, Fig 4)

Clinical observations There were no treatment- or dose-related clinical observations in either sex in any of the generations, except for transient evidence of dehydration at the start of the F0 prebreed in all groups, since some animals had difficulty adjusting to the automatic watering system, and at the start of the F1, F2, and F3 postwean (prebreed) exposure period at 7500 ppm, due to the small pups at this dose adjusting to the "nipples" of the automatic watering system, which was quickly resolved (data not presented)

Organ weights At necropsy, F0, F1, and F2 parental and F3 retained adult absolute nonreproductive organ weights were almost uniformly reduced for liver, kidneys, adrenal glands, spleen, pituitary, and brain at 7500 ppm (Table 2) Relative organ weights at 7500 ppm were typically significantly increased (or unaffected), with these effects most likely caused by reduced terminal body weights at this dietary dose Changes in absolute and relative organ weights did occur rarely in other groups, but they were not consistent across generations and did not exhibit a dose-response pattern (Table 2)

Histopathology There were no treatment- or dose-related gross or microscopic findings for the examined organs for F0, F1, and F2 parental animals, and for F3 retained adults at any concentration for either sex, except for slight to mild renal tubular degeneration and chronic hepatic inflammation observed at a higher incidence in F0, F1, and F2 (but not F3) females at 7500 ppm (Tables 3 and 4)

Parental Reproductive Parameters

Absence of effects For absolute or relative reproductive organ weights, there were no treatment-related effects at any concentration for either sex for any generation, except for significantly reduced absolute and relative paired ovary weights as discussed below There were no treatment- or dose-related direct effects in F0, F1, F2, and retained F3 males on absolute or relative weights of the testes, epididymides, prostate, or seminal vesicles plus coagulating glands (Table 2)

There were no effects of treatment in F0, F1, or F2 females on mating, fertility, pregnancy, or gestational indices, dead pups per litter, or percent postimplantation loss (prenatal mortality index, Table 5) Estrous cycle length in days was equivalent across all groups for F0, F1, F2, and F3 females Paired ovarian primordial follicle counts were similar between the

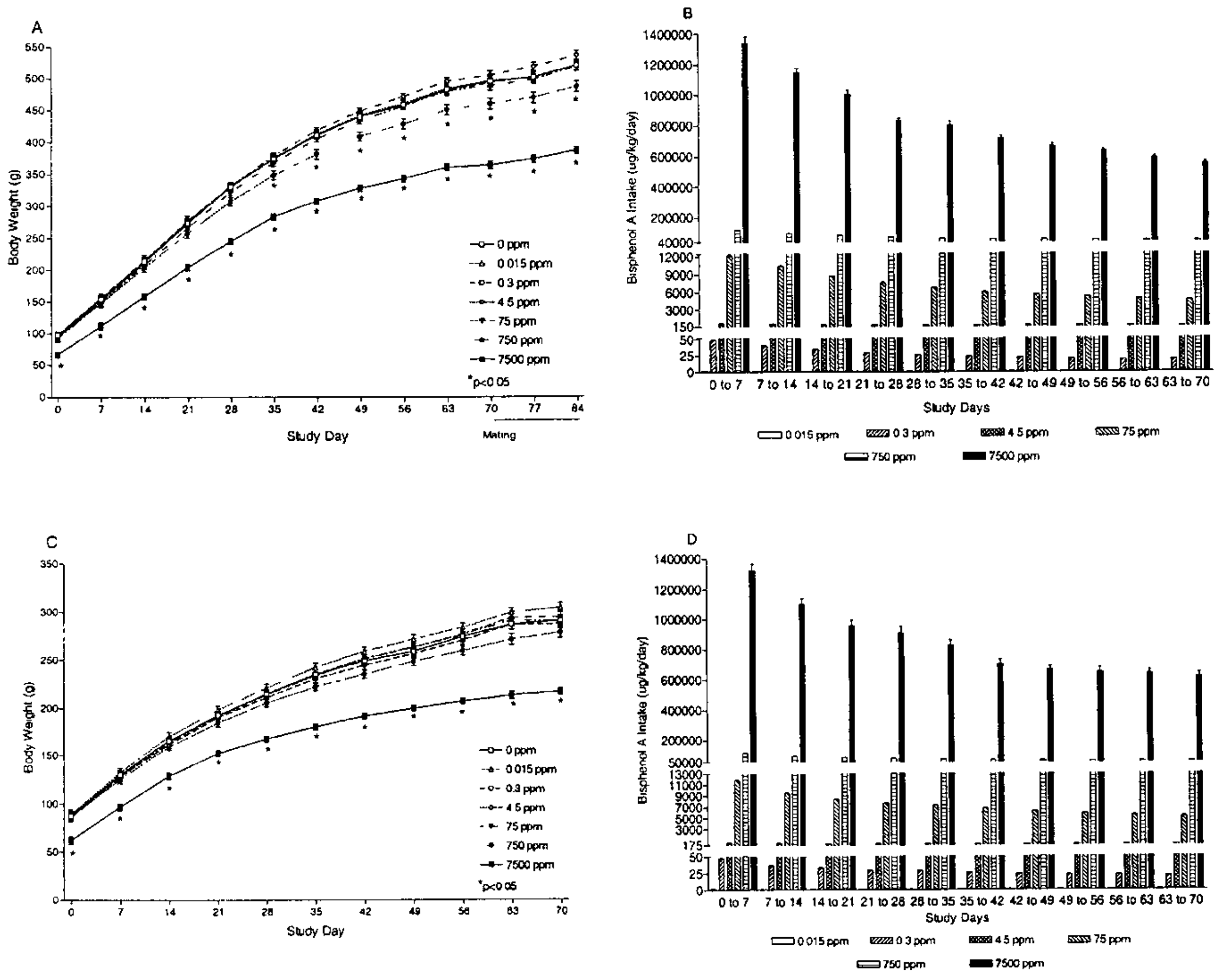

FIG. 3 Prebreed and mating body weights and BPA Intake for F1 animals (representative of all generations) (A) F1 male body weights during the prebreed and mating periods Data are presented as mean g ± SEM (B) F1 male BPA intake during the prebreed period Data are presented as mean μg/kg/day ± SEM (C) F1 female body weights during the prebreed period Data are presented as mean grams ± SEM Body weights were not taken for females during mating because of variable times to insemination (D) F1 female BPA intake during the prebreed period Data are presented as mean μg/kg/day ± SEM

high dose and control F1, F2, and F3 females (and increased at 7500 ppm for F0 females) Precoital interval in days and gestational length in days were equivalent across all groups for all generations

There were no effects of treatment in F0, F1, or F2 males on mating or fertility indices (data not shown) Also, there were no effects on epididymal sperm concentration (except for a significant reduction in epididymal sperm concentration in F1 males, but not F0, F2, or F3 males, at 7500 ppm), percent motile or progressively motile sperm, testicular homogenization-resistant spermatid head counts, DSP (except for a significant reduction in DSP at 7500 ppm for F3 males only), or efficiency of DSP in any generation of males (Table 5) Percent abnormal sperm was also unaffected for all F0, F1, F2, and F3 males in all groups Occasionally and sporadically, 1 male (or rarely 2) in some groups, in all generations, exhibited low motility and high incidence of abnormal sperm In every case for F0, F1, and F2 males (F3 males were not bred), the male sired a live litter

There were no treatment-related gross or microscopic findings in reproductive organs for F0, F1, F2, or F3 adult males or females in any group (Tables 3 and 4)

Presence of effects The only significant effects were seen primarily in the 7500 ppm group in both sexes There were significantly reduced absolute paired ovary weights in F0, F1, F2, and F3 females and relative paired ovary weights in F0, F1, and F2 (but not F3) females at 7500 ppm, in the presence of

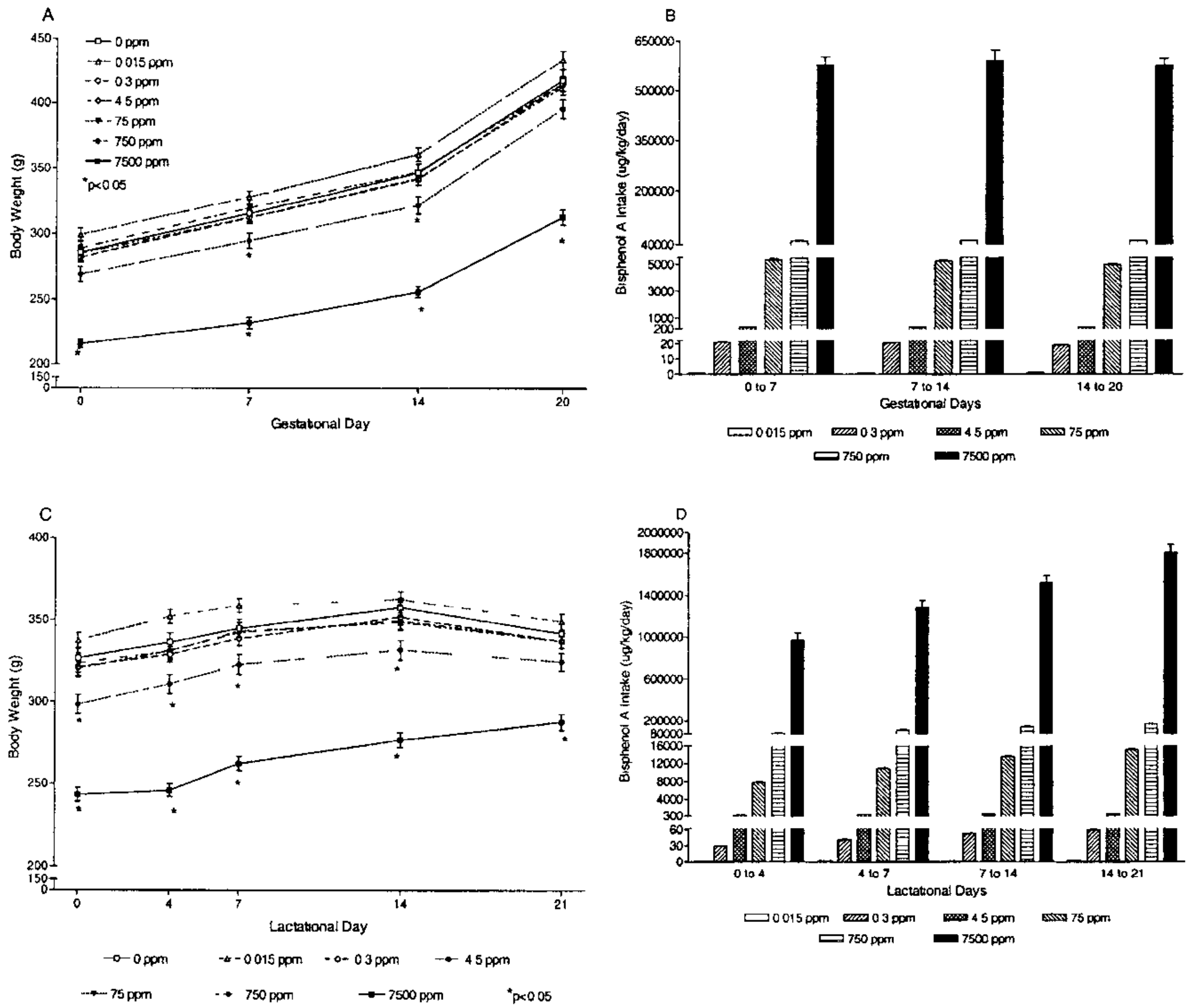

FIG. 4. Gestational and lactational body weights and BPA intake for F1 females (representative of all generations) (A) F1 female body weights during gestation Data are presented as mean g ± SEM (B) F1 female BPA intake during gestation Data are presented as mean µg/kg/day ± SEM (C) F1 female body weights during lactation Data are presented as mean g ± SEM (D) F1 female BPA intake during lactation Data are presented as mean µg/kg/day ± SEM

significant systemic maternal toxicity (Table 2). The only observed effects in F0, F1, F2, and retained F3 males were consistently reduced absolute organ weights and increased (or unaffected) relative organ weights, caused by the reduced terminal body weights of the males at 750 and 7500 ppm The number of implants, total pups, and live pups per litter at birth and on PND 4 precull were significantly reduced at 7500 ppm (500 mg/kg/day) for F1, F2, and F3 offspring (Tables 5 and 6)

Offspring Parameters

Absence of effects There were no differences among groups for F1, F2, or F3 stillbirth index (data not shown), prenatal (postimplantation) loss per litter (Table 5), sex ratio (% males) per litter at birth and throughout lactation (data not shown) or early postnatal (PND 0–4 precull) and lactational survival (PND 4 postcull–21) indices (Table 6) Interim offspring survival indices (PND 4–7, 7–14, and 14–21) were also unaffected (data not shown) In male offspring, there were no statistically significant effects on AGD, the number of nipples per pup, the number of areolae per pup, or the percent of pups with 1 or more nipples/areolae (Table 6)

Presence of effects Pup body weights per litter were reduced at 7500 ppm for F1, F2, and F3 offspring for the lactational period, measured on PND 7, 14, and 21 (Fig 5) For F1 litters, pup body weights per litter were also significantly reduced in the high dose group on PND 4 for all pups analyzed together, but not for sexes analyzed separately

TABLE 2
Summary of Selected F0, F1, and F2 Parental and Retained F3 Absolute (g) and Relative (% Sacrifice Weight) Organ Weights

Organ	Generation	BPA dietary concentration (ppm) 0	0.015	0.3	4.5	75	750	7500
Males								
Body weights (g)								
	F0	549.6 ± 9.0	538.8 ± 7.4	538.0 ± 8.5	552.4 ± 9.0	555.8 ± 10.1	528.3 ± 10.9	431.4 ± 6.4***
	F1	566.0 ± 10.0	565.1 ± 9.4	556.0 ± 8.8	580.2 ± 9.3	556.6 ± 8.1	532.7 ± 9.8*	416.6 ± 7.4***
	F2	591.5 ± 11.1	596.2 ± 9.6	568.7 ± 10.8	575.6 ± 10.1	567.1 ± 8.7	523.0 ± 8.2***	419.3 ± 7.0***
	F3	501.3 ± 7.5	505.5 ± 9.2	493.5 ± 8.7	506.2 ± 7.8	517.9 ± 9.8	476.0 ± 8.2	368.9 ± 5.0***
Liver (g)								
	F0	22.36 ± 0.58	22.14 ± 0.60	21.74 ± 0.53	22.50 ± 0.55	21.62 ± 0.55	19.80 ± 0.46**	16.79 ± 0.32***
	F1	23.17 ± 0.47	23.51 ± 0.52	23.29 ± 0.52	24.33 ± 0.50	23.11 ± 0.49	21.03 ± 0.48*	16.41 ± 0.38***
	F2	23.38 ± 0.75	23.68 ± 0.56	21.73 ± 0.42*	22.16 ± 0.57	21.80 ± 0.40	19.31 ± 0.50***	15.81 ± 0.36***
	F3	21.48 ± 0.54	21.62 ± 0.61	20.75 ± 0.55	22.15 ± 0.65	21.78 ± 0.54	18.61 ± 0.48**	15.03 ± 0.31***
Liver (% sacrifice weight)								
	F0	4.06 ± 0.07	4.10 ± 0.08	4.00 ± 0.07	4.07 ± 0.07	3.89 ± 0.07	3.75 ± 0.05**	3.89 ± 0.05
	F1	4.10 ± 0.05	4.15 ± 0.05	4.11 ± 0.06	4.21 ± 0.09	4.08 ± 0.05	3.95 ± 0.05	3.94 ± 0.06
	F2	3.93 ± 0.07	3.97 ± 0.06	3.83 ± 0.04	3.84 ± 0.06	3.85 ± 0.05	3.69 ± 0.06*	3.78 ± 0.07
	F3	4.28 ± 0.08	4.27 ± 0.08	4.20 ± 0.08	4.37 ± 0.10	4.20 ± 0.06	3.90 ± 0.06**	4.08 ± 0.07
Paired kidneys (g)								
	F0	4.35 ± 0.09	4.25 ± 0.10	4.42 ± 0.08	4.38 ± 0.08	4.42 ± 0.08	4.29 ± 0.09	3.86 ± 0.10***
	F1	4.55 ± 0.09	4.45 ± 0.07	4.44 ± 0.08	4.43 ± 0.08	4.53 ± 0.06	4.26 ± 0.11	3.70 ± 0.06***
	F2	4.38 ± 0.10	4.40 ± 0.07	4.25 ± 0.07	4.21 ± 0.07	4.20 ± 0.06	4.08 ± 0.09*	3.63 ± 0.08***
	F3	3.94 ± 0.06	4.00 ± 0.06	3.96 ± 0.08	4.02 ± 0.09	4.06 ± 0.07	3.76 ± 0.07	3.37 ± 0.05***
Paired kidneys (% sacrifice weight)								
	F0	0.79 ± 0.01	0.79 ± 0.02	0.82 ± 0.01	0.79 ± 0.01	0.80 ± 0.01	0.81 ± 0.01	0.90 ± 0.03***
	F1	0.81 ± 0.01	0.78 ± 0.01	0.79 ± 0.01	0.77 ± 0.01*	0.80 ± 0.01	0.80 ± 0.02	0.89 ± 0.01***
	F2	0.74 ± 0.01	0.74 ± 0.01	0.75 ± 0.01	0.73 ± 0.01	0.74 ± 0.01	0.78 ± 0.01*	0.87 ± 0.01***
	F3	0.79 ± 0.01	0.80 ± 0.01	0.80 ± 0.01	0.79 ± 0.01	0.79 ± 0.01	0.79 ± 0.01	0.92 ± 0.01***
Paired testes (g)								
	F0	3.48 ± 0.06	3.48 ± 0.06	3.43 ± 0.06	3.46 ± 0.05	3.46 ± 0.05	3.43 ± 0.04	3.43 ± 0.04
	F1	3.72 ± 0.05	3.57 ± 0.07	3.56 ± 0.06	3.56 ± 0.09	3.57 ± 0.05	3.56 ± 0.06	3.24 ± 0.05***
	F2	3.71 ± 0.05	3.59 ± 0.04	3.48 ± 0.05*	3.66 ± 0.06	3.67 ± 0.07	3.49 ± 0.05*	3.27 ± 0.05***
	F3	3.65 ± 0.04	3.44 ± 0.08*	3.35 ± 0.04**	3.50 ± 0.06	3.46 ± 0.06	3.30 ± 0.05***	3.19 ± 0.07***
Paired testes (% sacrifice weight)								
	F0	0.63 ± 0.01	0.65 ± 0.01	0.64 ± 0.01	0.63 ± 0.01	0.63 ± 0.01	0.66 ± 0.01	0.80 ± 0.01***
	F1	0.66 ± 0.01	0.64 ± 0.01	0.63 ± 0.01	0.62 ± 0.02	0.63 ± 0.01	0.67 ± 0.01	0.78 ± 0.02***
	F2	0.63 ± 0.01	0.61 ± 0.01	0.62 ± 0.01	0.64 ± 0.01	0.65 ± 0.01	0.67 ± 0.01	0.78 ± 0.01***
	F3	0.73 ± 0.01	0.69 ± 0.02	0.68 ± 0.01	0.70 ± 0.01	0.67 ± 0.01	0.70 ± 0.01	0.87 ± 0.02***
Paired epididymides (g)								
	F0	1.46 ± 0.03	1.42 ± 0.04	1.41 ± 0.02	1.43 ± 0.03	1.43 ± 0.02	1.41 ± 0.02	1.36 ± 0.02
	F1	1.45 ± 0.02	1.38 ± 0.02	1.42 ± 0.02	1.44 ± 0.02	1.41 ± 0.02	1.39 ± 0.02	1.30 ± 0.02***
	F2	1.45 ± 0.03	1.41 ± 0.03	1.40 ± 0.02	1.45 ± 0.02	1.41 ± 0.02	1.39 ± 0.02	1.31 ± 0.02***
	F3	1.34 ± 0.02	1.29 ± 0.03	1.29 ± 0.02	1.32 ± 0.02	1.28 ± 0.03	1.26 ± 0.02*	1.20 ± 0.02***
Paired epididymides (% sacrifice weight)								
	F0	0.27 ± 0.01	0.27 ± 0.01	0.26 ± 0.00	0.26 ± 0.01	0.26 ± 0.01	0.27 ± 0.01	0.32 ± 0.01***
	F1	0.26 ± 0.01	0.25 ± 0.00	0.25 ± 0.00	0.25 ± 0.01	0.25 ± 0.00	0.26 ± 0.00	0.31 ± 0.01***
	F2	0.25 ± 0.01	0.24 ± 0.01	0.25 ± 0.00	0.25 ± 0.00	0.25 ± 0.00	0.27 ± 0.00*	0.31 ± 0.00***
	F3	0.27 ± 0.01	0.26 ± 0.01	0.26 ± 0.01	0.26 ± 0.01	0.25 ± 0.00	0.27 ± 0.01	0.33 ± 0.01***
Prostate (g)								
	F0	1.05 ± 0.06	0.96 ± 0.04	0.94 ± 0.04	0.97 ± 0.05	0.94 ± 0.05	0.91 ± 0.04	0.73 ± 0.04***
	F1	0.73 ± 0.04	0.70 ± 0.03	0.72 ± 0.04	0.78 ± 0.04	0.79 ± 0.05	0.76 ± 0.04	0.58 ± 0.02*
	F2	0.65 ± 0.03	0.62 ± 0.02	0.59 ± 0.03	0.64 ± 0.02	0.60 ± 0.03	0.58 ± 0.02	0.49 ± 0.02***
	F3	0.56 ± 0.02	0.54 ± 0.02	0.60 ± 0.03	0.59 ± 0.03	0.62 ± 0.02	0.56 ± 0.03	0.42 ± 0.02***
Prostate (% sacrifice weight)								
	F0	0.19 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.01
	F1	0.13 ± 0.01	0.12 ± 0.00	0.13 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.14 ± 0.01
	F2	0.11 ± 0.01	0.10 ± 0.00	0.10 ± 0.01	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.12 ± 0.01
	F3	0.11 ± 0.00	0.11 ± 0.00	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.00	0.12 ± 0.01	0.11 ± 0.00
Preputial gland (g)								
	F0	0.24 ± 0.01	0.24 ± 0.01	0.23 ± 0.02	0.24 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.20 ± 0.01
	F1	0.23 ± 0.01	0.22 ± 0.02	0.20 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.18 ± 0.01*
	F2	0.22 ± 0.01	0.22 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.18 ± 0.01
	F3	0.19 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.23 ± 0.01	0.20 ± 0.01	0.19 ± 0.01	0.17 ± 0.01
Preputial gland (% sacrifice weight)								
	F0	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.05 ± 0.00	0.05 ± 0.00
	F1	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
	F2	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.03 ± 0.00	0.04 ± 0.00	0.04 ± 0.00
	F3	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.05 ± 0.00
Seminal vesicles with coagulating glands (g)								
	F0	2.24 ± 0.08	2.15 ± 0.09	2.34 ± 0.06	2.50 ± 0.07*	2.35 ± 0.06	2.33 ± 0.07	1.79 ± 0.07***
	F1	2.19 ± 0.07	2.10 ± 0.06	2.18 ± 0.06	2.20 ± 0.05	2.22 ± 0.05	2.13 ± 0.06	1.82 ± 0.07***
	F2	2.29 ± 0.07	2.12 ± 0.05	2.18 ± 0.06	2.34 ± 0.07	2.09 ± 0.07	2.22 ± 0.05	1.76 ± 0.07***
	F3	1.79 ± 0.06	1.85 ± 0.05	1.82 ± 0.06	1.93 ± 0.06	1.87 ± 0.05	1.70 ± 0.05	1.43 ± 0.05***

TABLE 2—*Continued*

Organ	Generation	BPA dietary concentration (ppm)						
		0	0.015	0.3	4.5	75	750	7500
Seminal vesicles with coagulating glands (% sacrifice weight)								
	F0	0.41 ± 0.01	0.40 ± 0.02	0.44 ± 0.01	0.45 ± 0.01	0.43 ± 0.01	0.45 ± 0.01	0.41 ± 0.02
	F1	0.39 ± 0.01	0.37 ± 0.01	0.39 ± 0.01	0.38 ± 0.01	0.39 ± 0.01	0.40 ± 0.01	0.44 ± 0.02*
	F2	0.39 ± 0.01	0.36 ± 0.01	0.39 ± 0.01	0.41 ± 0.01	0.37 ± 0.01	0.43 ± 0.01*	0.42 ± 0.02
	F3	0.36 ± 0.01	0.37 ± 0.01	0.37 ± 0.01	0.38 ± 0.01	0.36 ± 0.01	0.36 ± 0.01	0.39 ± 0.01
Females								
Body weight (g)								
	F0	327.6 ± 5.8	335.3 ± 4.9	329.5 ± 4.2	323.8 ± 6.3	324.4 ± 4.8	320.8 ± 4.4	285.1 ± 4.4***
	F1	339.4 ± 5.6	347.0 ± 4.5	335.3 ± 4.3	340.4 ± 5.2	335.7 ± 4.7	318.2 ± 5.0*	283.7 ± 5.4***
	F2	329.6 ± 5.2	338.7 ± 3.9	326.4 ± 5.9	322.0 ± 5.9	326.2 ± 4.8	321.2 ± 5.8	282.1 ± 4.0***
	F3	290.4 ± 3.9	302.9 ± 4.6	286.9 ± 6.6	293.5 ± 3.5	295.4 ± 3.5	282.9 ± 5.9	233.6 ± 4.9***
Liver (g)								
	F0	17.37 ± 0.51	18.07 ± 0.56	17.95 ± 0.38	17.71 ± 0.60	17.65 ± 0.46	17.25 ± 0.54	16.80 ± 0.57
	F1	18.55 ± 0.50	19.40 ± 0.52	18.86 ± 0.44	17.70 ± 0.59	17.49 ± 0.46	16.96 ± 0.51	16.66 ± 0.59
	F2	16.87 ± 0.36	19.94 ± 0.56***	16.57 ± 0.36	16.45 ± 0.46	16.98 ± 0.51	16.90 ± 0.49	17.34 ± 0.51
	F3	11.51 ± 0.21	11.92 ± 0.27	11.30 ± 0.29	12.11 ± 0.36	11.55 ± 0.24	11.00 ± 0.28	9.54 ± 0.21***
Liver (% sacrifice weight)								
	F0	5.29 ± 0.12	5.37 ± 0.12	5.45 ± 0.10	5.47 ± 0.13	5.43 ± 0.14	5.36 ± 0.14	5.87 ± 0.15**
	F1	5.46 ± 0.13	5.58 ± 0.11	5.63 ± 0.12	5.22 ± 0.17	5.21 ± 0.12	5.33 ± 0.14	5.85 ± 0.16
	F2	5.13 ± 0.09	5.92 ± 0.19***	5.10 ± 0.11	5.14 ± 0.15	5.21 ± 0.14	5.28 ± 0.15	6.12 ± 0.13***
	F3	3.96 ± 0.05	3.93 ± 0.06	3.93 ± 0.06	4.12 ± 0.06	3.91 ± 0.06	3.86 ± 0.05	4.09 ± 0.05
Paired kidneys (g)								
	F0	2.84 ± 0.06	2.89 ± 0.06	2.94 ± 0.04	2.69 ± 0.06	2.82 ± 0.05	2.76 ± 0.05	2.63 ± 0.05*
	F1	2.98 ± 0.06	3.11 ± 0.04	3.02 ± 0.04	2.94 ± 0.05	2.96 ± 0.05	2.86 ± 0.05	2.55 ± 0.06***
	F2	2.94 ± 0.05	2.98 ± 0.04	2.87 ± 0.05	2.82 ± 0.04	2.85 ± 0.05	2.81 ± 0.06	2.66 ± 0.05***
	F3	2.35 ± 0.04	2.38 ± 0.04	2.29 ± 0.04	2.33 ± 0.05	2.39 ± 0.04	2.31 ± 0.04	1.93 ± 0.04***
Paired kidneys (% sacrifice weight)								
	F0	0.87 ± 0.01	0.86 ± 0.01	0.89 ± 0.01	0.84 ± 0.02	0.87 ± 0.01	0.86 ± 0.01	0.93 ± 0.01*
	F1	0.88 ± 0.01	0.90 ± 0.01	0.90 ± 0.01	0.87 ± 0.01	0.88 ± 0.02	0.90 ± 0.01	0.90 ± 0.01
	F2	0.89 ± 0.01	0.88 ± 0.01	0.88 ± 0.01	0.88 ± 0.01	0.87 ± 0.01	0.88 ± 0.01	0.94 ± 0.01*
	F3	0.81 ± 0.01	0.79 ± 0.01	0.80 ± 0.01	0.80 ± 0.01	0.81 ± 0.01	0.82 ± 0.01	0.83 ± 0.01
Paired ovaries (g)								
	F0	0.17 ± 0.01	0.16 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.00	0.16 ± 0.01	0.12 ± 0.00***
	F1	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.16 ± 0.01*	0.13 ± 0.01***
	F2	0.18 ± 0.01	0.15 ± 0.01*	0.16 ± 0.01	0.15 ± 0.01***	0.15 ± 0.00*	0.16 ± 0.00	0.12 ± 0.00***
	F3	0.14 ± 0.01	0.13 ± 0.00	0.14 ± 0.00	0.13 ± 0.00	0.14 ± 0.01	0.14 ± 0.00	0.12 ± 0.00**
Paired ovaries (% sacrifice weight)								
	F0	0.052 ± 0.002	0.049 ± 0.002	0.051 ± 0.002	0.054 ± 0.002	0.053 ± 0.002	0.050 ± 0.002	0.042 ± 0.001***
	F1	0.053 ± 0.002	0.051 ± 0.002	0.053 ± 0.001	0.052 ± 0.002	0.053 ± 0.002	0.049 ± 0.001	0.045 ± 0.002**
	F2	0.054 ± 0.002	0.046 ± 0.001**	0.049 ± 0.002	0.046 ± 0.002**	0.048 ± 0.001*	0.049 ± 0.001	0.041 ± 0.002***
	F3	0.048 ± 0.002	0.043 ± 0.002	0.047 ± 0.002	0.046 ± 0.002	0.046 ± 0.002	0.049 ± 0.001	0.051 ± 0.002
Uterus (g)								
	F0	0.75 ± 0.03	0.63 ± 0.03*	0.73 ± 0.05	0.67 ± 0.03	0.68 ± 0.03	0.68 ± 0.03	0.58 ± 0.03***
	F1	0.66 ± 0.04	0.60 ± 0.02	0.63 ± 0.03	0.60 ± 0.03	0.61 ± 0.02	0.63 ± 0.03	0.51 ± 0.02**
	F2	0.89 ± 0.16	0.78 ± 0.04	0.68 ± 0.03	0.70 ± 0.04	0.75 ± 0.04	0.76 ± 0.04	0.58 ± 0.02*
	F3	0.67 ± 0.04	0.66 ± 0.03	0.71 ± 0.04	0.68 ± 0.03	0.68 ± 0.03	0.69 ± 0.03	0.62 ± 0.03
Uterus (% sacrifice weight)								
	F0	0.23 ± 0.01	0.19 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.21 ± 0.01	0.21 ± 0.01	0.20 ± 0.01
	F1	0.20 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.20 ± 0.01	0.18 ± 0.01
	F2	0.26 ± 0.04	0.23 ± 0.01	0.21 ± 0.01	0.22 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.21 ± 0.01
	F3	0.23 ± 0.01	0.22 ± 0.01	0.25 ± 0.02	0.23 ± 0.01	0.23 ± 0.01	0.25 ± 0.01	0.27 ± 0.02

Note Additional organs evaluated included adrenal glands, spleen, brain, and pituitary gland (data not shown)
*$p < 0.05$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM
**$p < 0.01$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM
***$p < 0.001$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM

In female offspring, AGD was significantly increased in the F2 generation at all dietary doses, with the exception of the 75 and 7500 ppm groups (Table 6, Fig 8) The absolute age at VP (days) was significantly delayed in the F1, F2, and F3 generations at 7500 ppm (and at 75 ppm only for the F2 generation) When the age at acquisition was adjusted for the body weight at acquisition, VP was delayed only at 7500 ppm for all 3 offspring generations When the age at acquisition was adjusted for the body weight on SD 7, VP was delayed at 7500 ppm for the F1 and F3 generations and unaffected in the F2 generations (see Discussion, Table 6, Fig. 7)

In male offspring, the absolute age at PPS (days) was significantly delayed in the F1 generation at 750 and 7500 ppm, in the F2 generation at 0 3, 75, 750, and 7500 ppm, and in the F3 generation at 7500 ppm When the age at acquisition was adjusted for the body weight at acquisition, PPS was delayed in the F1 generation at 750 and 7500 ppm and in the F2 and F3 generations at 7500 ppm When the age at acquisition was

TABLE 3
Histopathologic Findings in Organs from F0, F1, F2, and F3 Adult Males

	F0							F1							F2							F3						
Dose group	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Adrenal glands																												
No examined	28	14	12	13	14	12	11	30	10	10	10	10	10	10	30	10	10	10	10	11	10	30	10	11	10	10	10	10
Cortex degeneration	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	1	—	—	—	—
Hypoplasia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Coagulating glands																												
No examined	30	15	12	15	17	15	11	30	13	13	19	14	13	11	30	15	14	19	17	16	14	30	10	11	10	10	10	10
Chronic inflammation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Epididymis																												
No examined	30	15	12	15	17	15	11	30	13	13	19	14	13	11	30	15	14	19	17	16	13	30	10	11	10	10	10	10
Chronic inflammation	—	—	1	—	—	—	1	—	—	1	—	1	—	—	1	1	—	—	1	1	—	3	1	—	2	—	—	2
Hypospermia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	1	—	—	—	—	—
Tubule giant cells	1	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tubule aspermia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Tubule hypospermia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Kidneys																												
No examined	30	14	12	13	14	12	11	30	10	10	10	10	10	10	30	10	10	10	10	11	10	30	10	11	10	10	10	10
Cortex, cyst(s)	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cortex dilatation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cortex chronic inflammation	2	—	—	—	—	—	—	3	—	—	—	1	—	—	3	1	—	—	1	—	1	1	—	—	1	—	2	—
Epithelium, karyomegaly	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medullary cyst(s)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3	—	—	—	1	—	3
Hydronephrosis	—	1	—	—	—	—	—	3	—	1	—	2	1	1	5	1	1	2	1	—	—	5	—	—	—	—	1	—
Mineralization[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3
Medulla dilatation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medulla inflamm , chronic	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Nephropathy	11	4	7	6	6	3	3	15	9	6	5	[illegible]	4	3	9	4	7	4	3	5	5	12	7	6	4	8	2	3
Pelvis inflammation chronic	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pelvis microcalcus	2	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pyelonephritis, chronic	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Renal tubule dilatation	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Renal tubule[b]	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Liver																												
No examined	30	14	12	13	14	12	11	30	10	10	10	10	10	10	30	10	10	10	10	11	10	30	10	11	10	10	10	10
Artery inflammation chronic	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Clear cell focus	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hepatocyte necrosis	—	—	—	1	—	—	—	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation chronic	—	—	—	1	—	—	2	1	—	—	—	—	—	1	11	3	3	2	2	3	2	4	—	1	1	1	3	3
Malignant lymphoma	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Pituitary gland																												
No examined	27	13	12	11	14	12	10	30	10	9	10	10	10	10	29	10	10	10	8	10	9	29	10	11	10	10	10	10
Pars distalis, cyst(s)	2	2	—	—	—	—	—	2	—	—	—	1	—	—	—	—	1	—	—	—	—	2	3	—	1	—	—	—
Pars distalis hyperplasia	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pars distalis degeneration	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Pars intermedia cyst(s)	—	—	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pars nervosa[c]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pars distalis lymphoma	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Preputial gland																												
No examined	30	14	12	15	15	15	11	29	13	13	19	14	13	11	30	15	14	19	16	15	13	29	10	11	9	10	10	9
Hyperplasia	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation, chronic	27	12	12	8	11	13	8	21	8	11	13	11	6	7	22	13	9	12	13	11	10	17	8	4	8	8	6	9
Periglandular inflamm acute	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Prostate																												
No examined	30	15	11	15	17	15	11	29	13	13	19	14	13	11	30	14	14	19	17	16	14	30	10	11	10	10	10	10
Abscess	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation, chronic	6	3	4	8	6	7	2	11	3	4	8	4	6	3	15	7	7	10	8	5	3	18	5	6	7	4	7	2
Seminal vesicles																												
No examined	30	15	12	15	17	15	11	30	13	13	19	14	13	11	30	15	14	19	17	16	13	30	10	11	10	10	10	10
Inflammation, acute	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation chronic	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Spleen																												
No examined	30	14	12	13	14	12	11	30	10	10	10	10	10	10	30	10	10	10	10	11	10	30	10	11	10	10	10	10
Fibrosis capsule	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
Lymphoid hyperplasia	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Malignant lymphoma	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
White pulp, depletion	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
Testis (left)																												
No examined	30	15	12	15	17	15	11	30	13	13	19	14	13	11	30	15	14	19	17	16	14	30	10	11	10	10	10	10
Atrophy, seminif tubule	3	1	—	1	—	1	—	—	—	—	1	—	—	1	2	1	—	—	—	—	—	—	1	—	—	—	1	1
Degeneration seminif tubule	3	1	1	3	2	1	—	1	—	1	—	—	—	1	1	—	—	—	—	—	1	1	1	—	—	—	1	—
Urinary bladder																												
No examined	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation chronic	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Note Dose groups 1 = 0 0 ppm (control), 2 = 0 015 ppm, 3 = 0 3 ppm, 4 = 4 5 ppm, 5 = 75 ppm, 6 = 750 ppm, 7 = 7500 ppm —, no finding
[a] Corticomedullary junction
[b] Vacuolization, cytoplasmic, epithelial
[c] Developmental malformation

adjusted for the body weight on SD 14, nothing changed (PPS was delayed at 750 and 7500 ppm for the F1 generation and at 7500 ppm for the F2 and F3 generations, see Discussion, Table 6, Fig. 7).

For F1, F2, and F3 weanling males and females sacrificed on PND 21, the absolute organ weights were decreased at 7500 ppm (the dietary concentration at which the terminal body weights were also decreased, data not shown). There were reductions in absolute organ weights at lower doses, but they were not consistently affected in F1, F2, and F3 weanlings or reproducible in specific dose groups. Relative organ weights were increased (or unaffected) at 7500 ppm (again, caused by reduced body weights at this dietary dose).

DISCUSSION

This study evaluated exposure of CD (SD) rats to BPA administered in the diet *ad libitum* at 0, 0.015, 0.3, 4.5, 75, 750, and 7500 ppm (approximate BPA intakes of 0, 0.001 [1 μg/kg/day], 0.02 [20 μg/kg/day], 0.3 [300 μg/kg/day], 5, 50, and 500 mg/kg/day, respectively) for 3 offspring generations, 1 litter per generation, through F3 adulthood. In the more than one million measurements made in this study, the number of significant, treatment-related effects was extremely small. The vast majority of parameters measured was within the concurrent and historical control ranges and, thus, are only briefly discussed. The focus of this discussion is to address those few endpoints that appeared to be either statistically significant and/or of possible biological significance.

Parental Systemic Parameters

Systemic toxicity effects in adult animals were limited to reductions in body weight, weight gain, and feed consumption in the top 2 doses (750 and 7500 ppm).

At 7500 ppm, there were consistent and persistent reductions in body weights and weight gains in both sexes and in F0, F1, F2, and F3 generations. Feed consumption in g/day and g/kg/day was variable and showed no clear treatment-related effects, nor were there treatment- or dose-related clinical observations in either sex in any generation. Body weights during gestation and lactation were significantly reduced in F0, F1, and F2 females at 7500 ppm, in F0 and F2 females at 750 ppm, and at 750 ppm in F1 females during lactation.

At necropsy, F0, F1, and F2 parental and F3 retained adult absolute organ weights were almost uniformly reduced for liver, kidneys, adrenal glands, spleen, pituitary, and brain at 7500 ppm. Relative organ weights at 7500 ppm were typically significantly increased, with both effects most likely caused by the reduced terminal body weights at this dietary dose. There were no treatment- or dose-related gross or microscopic findings for the examined organs in any parental animal, except for renal tubular degeneration and chronic hepatic inflammation observed at a higher incidence in F0, F1, and F2 (but not F3) females at 7500 ppm. There were no toxicologically significant effects on these parameters at 75 ppm or below.

Parental Reproductive Parameters

There were no effects of treatment in F0, F1, or F2 females on mating, fertility, pregnancy or gestational indices, dead pups per litter, or of percent postimplantation loss (prenatal mortality index). There were no treatment-related effects on absolute or relative reproductive organ weights, except for significantly reduced paired ovary weights (see below). Estrous cycle length in days was equivalent across all groups for F0, F1, F2, and F3 females. Paired ovarian primordial follicle counts were similar between the high dose and control F1, F2, and F3 females (but increased at 7500 ppm for F0 females). Precoital interval in days and gestational length in days were equivalent across all groups for all generations.

There were no effects of treatment in F0, F1, or F2 males on mating or fertility indices, or treatment- or dose-related direct effects in F0, F1, F2 and retained F3 males on absolute or relative weights of the testes, epididymides, prostate, or seminal vesicles plus coagulating glands. Also, there were no effects on epididymal sperm concentration (except for a significant reduction in epididymal sperm concentration in F1 males, but not F0, F2, and F3 males, at 7500 ppm), percent motile or progressively motile sperm, testicular homogenization-resistant spermatid head counts, DSP (except for a significant reduction in DSP at 7500 ppm for F3 males, but not F0, F1, or F2 males, with no effect on efficiency of DSP), or efficiency of DSP. Percent abnormal sperm was also unaffected for all F0, F1, F2, and F3 males in all groups. The slightly higher (but not statistically significant) values for F2 males at 0.015, 0.3, 4.5, and 75 ppm and for F3 males at 0.015 and 75 ppm were due to 1 or 2 males per group with few or no motile sperm and most or all abnormal sperm. In all cases for the F2 males, the affected males sired live litters (F3 males were not bred). There were no treatment-related gross or microscopic findings on reproductive organs for F0, F1, F2, or F3 adult males or females.

The vast majority of the relatively few effects observed for parental reproductive parameters occurred only at the highest dose of 7500 ppm. The number of implants, total pups, and live pups per litter at birth and on PND 4 precull were significantly reduced at 7500 ppm for F1, F2, and F3 offspring.

The explanation for the reduced live litter size at birth at 7500 ppm for F1, F2, and F3 offspring is not known. It is not due to the male since there is no evidence of reproductive effects on the males at 7500 ppm (or any other dietary dose), nor is it due to prenatal postimplantation loss of conceptuses, since postimplantation loss was unaffected at any dose for F0, F1, and F2 dams carrying F1, F2, and F3 litters. Preimplantation loss cannot be determined from this study design since, by the time the parental females are sacrificed, the ovarian corpora lutea of pregnancy (which form after ovulation) have involuted

TABLE 4
Histopathologic Findings in Organs from F0, F1, F2, and F3 Adult Females

	F0							F1							F2							F3						
Dose group	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Adrenal glands																												
No examined	30	12	12	12	14	12	13	30	10	10	10	10	10	11	30	11	10	12	11	12	13	30	10	10	10	9	10	10
Cortex, degeneration	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Cervix																												
No examined	30	13	14	14	16	14	13	28	10	10	13	13	14	10	30	10	12	14	12	13	15	30	10	8	7	9	10	10
Inflammation, chronic	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Kidneys																												
No examined	30	12	12	12	14	12	13	30	10	10	10	10	10	11	30	11	10	12	11	12	13	30	10	10	10	10	10	10
Cortex cyst(s)	—	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cortex, inflammation chronic	—	—	—	1	1	—	—	1	—	1	—	1	1	1	1	—	—	—	—	—	—	2	—	1	—	—	1	—
Hydronephrosis	1	—	—	—	—	—	—	1	—	—	1	1	—	—	1	—	—	—	—	—	—	—	1	—	—	1	1	—
Medulla, cyst(s)	—	—	—	—	1	—	—	—	—	—	1	1	—	—	1	—	—	—	—	—	1	1	1	—	—	—	—	—
Medulla, inflammation, chronic	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	1	—	—	—	—	—	—	—
Mineralization[a]	0	6	3	8	7	7	1	2	1	6	2	2	1	1	7	2	2	2	2	2	—	8	1	2	2	5	1	—
Nephropathy	3	2	3	1	2	2	—	2	—	1	2	—	—	—	6	1	—	2	2	2	2	3	—	—	3	—	1	2
Papilla, degeneration	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Papilla, inflammation acute	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Papilla, inflammation, chronic	—	—	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—
Papilla, mineralization	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—
Pelvis calcus	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Pelvis inflammation, chronic	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Pyelonephritis, chronic	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Renal tubule, degeneration	—	—	—	—	—	—	4	—	—	—	—	—	—	8	—	—	—	—	—	—	7	—	—	—	—	—	—	—
Renal tubule, regeneration	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Liver																												
No examined	30	12	12	12	14	12	13	30	10	10	10	10	10	11	30	11	10	12	11	12	13	30	10	10	10	10	10	10
Bile duct, hyperplasia	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Clear cell focus	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hepatocyte degeneration	—	—	—	—	—	—	—	—	—	—		—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
Hepatocyte necrosis	1	1	1		—	1	—	—	—	—		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation chronic	—	—	1	—	—	1	3	3	—	—	3	1	1	3	3	1	—	2	2	2	5	4	1	1	1	4	1	1
Malignant lymphoma	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—
Ovary																												
No examined	29	12	14	13	16	14	13	30	10	10	13	13	14	12	30	13	12	14	12	14	16	30	10	10	10	10	10	10
Atrophy	1	1	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	1	—	—
Follicle, cyst(s)	2	1	2	1	—	—	—	3	2	1	—	1	1	—	2	—	—	—	—	1	—	—	—	—	1	—	—	—
Testes[c]	—	—	—	—	—	—	—	—	—	—		—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Oviduct																												
No examined	29	12	14	13	16	14	13	30	10	10	13	13	14	11	30	13	12	14	12	14	16	30	10	10	10	10	10	10
Dilatation	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pituitary																												
No examined	30	12	11	12	14	12	13	28	10	9	10	10	8	10	30	11	10	12	11	12	12	30	10	10	10	10	10	10
Hyperplasia	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pars distalis, cyst(s)	3	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Pars distalis hyperplasia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Spleen																												
No examined	30	12	12	12	14	12	13	30	10	10	10	10	10	11	30	11	10	12	11	12	13	30	10	10	10	10	10	10
Lymphoid depletion	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Malignant lymphoma	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—
White pulp, depletion	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
Urinary bladder																												
No examined	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, chronic	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Uterus																												
No examined	30	13	14	14	15	14	13	30	10	10	13	13	14	10	30	13	12	15	12	14	16	30	10	10	9	10	10	10
Decidual reaction	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Hydrometra	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Hypoplasia		—			—	—		—	—	—	—	—	—		—		—	1	—	—	—	—	—	—	—	—	—	—
Inflammation, acute	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inflammation, chronic	—	—	1	—	—	—	—	—	—	—	—	—	—	—	1		—	—	—	—	—	—	—	—	—	—	—	—

TABLE 4—*Continued*

Dose group	F0							F1							F2							F3						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Vagina																												
No. examined	30	13	14	14	16	14	13	29	10	10	12	13	14	10	30	12	12	15	12	13	16	30	10	10	10	9	10	10
Hypoplasia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Inflammation, chronic	—	—	—	—	—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—
Squamous cyst(s)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Systemic neoplasms[c]																												
No. examined																						30	10	10	10	10	10	10
Malignant lymphoma																						—	—	—	1	—	—	—

Note. Dose groups: 1 = 0.0 ppm (control), 2 = 0.015 ppm, 3 = 0.3 ppm, 4 = 4.5 ppm, 5 = 75 ppm, 6 = 750 ppm, 7 = 7500 ppm. —, no finding.
[a]Corticomedullary junction.
[b]Developmental malformation: F1 animal no. 1214 at 7500 ppm was identified as a female at birth (based on AGD) and throughout in-life. At scheduled necropsy, no. 1214 exhibited midabdominal testes with no male accessory sex organs and no female reproductive organs (confirmed histopathologically). All of the siblings of no. 1214 exhibited normal reproductive structures. This animal's male sibling (no. 1221) was also retained postweaning and produced a live F2 litter. The F2 retained offspring of no. 1221 also produced live F3 litters. The most likely interpretation is that no. 1214 is a spontaneous genetic male pseudohermaphrodite, a mutation that is relatively common in mammals, including humans (Quigley *et al.*, 1995).
[c]Systemic neoplasm only reported for F3 females, although there were malignant lymphomas reported in various tissues for F1 and F2 males (but not F0 or F3 males) and for F3 females (but not for F0, F1, or F2 females). None appeared to be treatment or dose related.

to corpora albicans, indistinguishable from corpora albicans from previous ovulation cycles. Although the absolute and relative paired ovarian weights were reduced in F0, F1, F2, and F3 (absolute only) females in the present study, there was no evidence of reduced ovarian primordial follicle counts at 7500 ppm in any generation, even in the presence of significant systemic maternal toxicity.

There were no significant histopathological findings for any reproductive organ in either sex at any dose in any generation.

Offspring Parameters

As in the parental animals, the vast majority of the relatively few effects observed for offspring parameters occurred only at the highest dose of 7500 ppm.

Body weights. Effects on body weights were also observed in offspring only at 7500 ppm, beginning on PND 7 and continuing through lactation, weaning, and the postweaning period to adulthood in all 3 generations (F1, F2, and F3). The reduced body weight in periweanlings at 7500 ppm and in older animals at 750 and 7500 ppm, in all generations, was most likely the cause of the reduced absolute organ weights in F1, F2, and F3 weanlings, F1, F2, and F3 adults, and consistent with the increased (or absence of an effect on) relative organ weights at these dietary doses.

Organ weights. Absolute and relative organ weight data for F1, F2, and F3 weanling (PND 21) pups indicate that for all but the ovaries, the absolute organ weights were reduced, and the relative organ weights were increased or unaffected in all groups, including 750 and 7500 ppm, at which postweaning body weights were significantly reduced. For paired ovary weights, the effects in the F1, F2, and F3 female weanlings at 7500 ppm paralleled effects observed in the F0, F1, and F2 adult females (both absolute and relative weights were reduced) and in the F3 adult females (only absolute ovary weights were reduced). For F1, F2, and F3 males and females, the absolute organ weight changes were decreased at 7500 ppm (the dietary concentration at which the terminal body weights were also decreased). At 7500 ppm, there were reductions in absolute and relative paired ovarian weights (absolute in F1, F2, and F3 females, relative in F1 and F2, but not F3, females). Statistical analysis of ovary weight, covaried by body weight at necropsy (Fig. 6A), indicated consistent effects only at 7500 ppm. Similarly, testis weight covaried by body weight at necropsy (Fig. 6B) indicated effects only in the F3 generation (the generation not mated), with no effects in the F0, F1, or F2 generation males.

Some of the effects on absolute or relative organ weights in the F1, F2, and F3 weanlings were also present in the corresponding adults, including absolute and relative paired ovary weights that were significantly reduced in the weanling and adult F1, F2, and F3 females at 7500 ppm. The patterns of absolute and relative weights show that test material-related effects exist only in the highest dose group and only for paired ovaries.

In accordance with current thinking on absolute and relative organ weights, when terminal body weights are reduced, only those organ weight parameters that exhibit statistically significant differences in the same direction for both absolute and relative values are considered biologically important and directly treatment related. Therefore, the changes in relative F1, F2, and F3 male and female weanling organ weights were not considered to be biologically significant and were most likely

TABLE 5
Summary of Selected F0, F1, and F2 Male and Female Reproductive Parameters

Generation	BPA dietary concentration (ppm)						
	0	0.015	0.3	4.5	75	750	7500
Females							
Estrous cycle length (days)							
F0	4.58 ± 0.25	4.41 ± 0.09	4.48 ± 0.20	4.50 ± 0.11	4.57 ± 0.14	4.45 ± 0.18	4.26 ± 0.09
F1	4.41 ± 0.10	4.47 ± 0.13	4.19 ± 0.09	4.70 ± 0.23	4.94 ± 0.21	4.40 ± 0.13	4.54 ± 0.11
F2	4.54 ± 0.21	4.61 ± 0.24	4.39 ± 0.14	4.47 ± 0.23	4.17 ± 0.07	4.56 ± 0.24	4.56 ± 0.11
F3	4.32 ± 0.18	4.34 ± 0.12	4.32 ± 0.09	4.39 ± 0.18	4.66 ± 0.21	4.59 ± 0.21	4.31 ± 0.09
Precoital interval (days)							
F0	2.3 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.9 ± 0.3	2.4 ± 0.2	2.3 ± 0.2	3.4 ± 0.5
F1	3.0 ± 0.4	3.2 ± 0.3	2.7 ± 0.2	3.1 ± 0.4	3.1 ± 0.4	2.8 ± 0.3	2.7 ± 0.2
F2	3.1 ± 0.4	2.0 ± 0.2	2.8 ± 0.5	2.7 ± 0.3	2.9 ± 0.3	2.7 ± 0.2	3.1 ± 0.3
Gestational length (days)							
F0	22.1 ± 0.1	22.1 ± 0.1	22.1 ± 0.1	22.1 ± 0.1	22.2 ± 0.1	22.0 ± 0.1	22.1 ± 0.1
F1	21.8 ± 0.1	22.0 ± 0.1	21.9 ± 0.1	22.0 ± 0.1	21.9 ± 0.1	22.0 ± 0.1	21.8 ± 0.1
F2	22.0 ± 0.1	22.3 ± 0.1	22.0 ± 0.1	22.0 ± 0.3	22.1 ± 0.1	22.0 ± 0.1	22.1 ± 0.1
No. implant sites/dam							
F0	14.23 ± 0.62	15.04 ± 0.51	14.93 ± 0.49	13.93 ± 0.61	14.74 ± 0.64	14.04 ± 0.48	11.89 ± 0.52**
F1	15.86 ± 0.44	16.33 ± 0.46	15.13 ± 0.64	14.85 ± 0.79	15.33 ± 0.39	16.00 ± 0.38	11.93 ± 0.43***
F2	15.25 ± 0.33	15.03 ± 0.38	14.03 ± 0.53*	14.19 ± 0.73	15.11 ± 0.39	14.44 ± 0.33	12.44 ± 0.29***
No. total pups/litter							
F1	14.4 ± 0.6	14.9 ± 0.7	14.3 ± 0.5	13.5 ± 0.6	14.0 ± 0.5	13.1 ± 0.6	11.8 ± 0.4**
F2	14.9 ± 0.6	15.1 ± 0.5	14.5 ± 0.7	14.7 ± 0.7	14.5 ± 0.5	15.0 ± 0.5	11.1 ± 0.5***
F3	14.9 ± 0.4	14.3 ± 0.4	13.3 ± 0.5*	13.8 ± 0.6	14.1 ± 0.4	13.8 ± 0.4	11.2 ± 0.4***
% Postimplantation loss/litter							
F1	3.45 ± 1.23	6.96 ± 2.67	7.02 ± 1.70	5.66 ± 1.48	13.81 ± 4.21	9.96 ± 3.03	11.33 ± 3.64
F2	9.35 ± 1.83	9.11 ± 1.51	7.59 ± 1.97	6.44 ± 1.70	7.04 ± 1.44	7.37 ± 1.98	11.08 ± 2.21
F3	5.02 ± 1.14	7.17 ± 1.60	6.59 ± 1.57	10.88 ± 3.92	9.26 ± 1.77	6.87 ± 1.35	12.30 ± 2.17
Paired ovarian primordial follicle counts							
F0	315.9 ± 41.6						453.2 ± 26.3*
F1	353.0 ± 35.4						409.7 ± 46.8
F2	409.2 ± 32.7						378.0 ± 25.5
F3	384.6 ± 55.7						355.4 ± 38.3
Males							
Epididymal sperm concentration (10^6/g)							
F0	813.14 ± 38.97	769.90 ± 36.76	752.69 ± 26.03	840.46 ± 29.09	775.56 ± 37.65	742.48 ± 30.46	755.52 ± 29.23
F1	682.60 ± 33.25	645.25 ± 25.65	648.58 ± 28.48	653.18 ± 23.38	654.20 ± 20.86	621.57 ± 26.29	557.31 ± 27.72**
F2	924.19 ± 25.22	908.42 ± 35.65	907.95 ± 28.28	894.06 ± 24.36	860.14 ± 31.97	905.91 ± 24.93	877.38 ± 29.13
F3	899.10 ± 28.55	897.19 ± 38.31	911.87 ± 35.47	923.84 ± 29.24	860.96 ± 31.93	929.36 ± 31.70	867.95 ± 27.80
Sperm motility (%)							
F0	77.5 ± 2.1	77.7 ± 3.0	78.4 ± 1.5	76.9 ± 1.8	78.3 ± 2.9	77.9 ± 1.4	79.1 ± 1.5
F1	79.4 ± 1.0	78.6 ± 1.7	79.9 ± 1.4	79.0 ± 1.4	79.3 ± 1.5	81.0 ± 0.9	79.2 ± 1.2
F2	79.0 ± 1.4	76.1 ± 2.9	76.8 ± 1.6	76.3 ± 2.1	77.0 ± 1.4	79.7 ± 1.2	78.6 ± 1.0
F3	72.4 ± 1.8	69.8 ± 3.0	70.1 ± 2.0	73.4 ± 1.9	68.2 ± 3.0	68.1 ± 2.0	74.6 ± 1.8
% Abnormal sperm							
F0	3.29 ± 0.92	1.72 ± 0.21	2.01 ± 0.24	2.03 ± 0.28	5.16 ± 3.27	2.35 ± 0.71	1.70 ± 0.16
F1	1.98 ± 0.16	4.13 ± 2.20	3.44 ± 1.28	1.98 ± 0.15	2.41 ± 0.45	1.82 ± 0.16	1.91 ± 0.18
F2	2.19 ± 0.38	4.89 ± 2.99	4.10 ± 2.30	3.25 ± 1.39	3.47 ± 1.12	2.05 ± 0.25	1.62 ± 0.17
F3	1.75 ± 0.16	5.14 ± 3.23	1.93 ± 0.20	2.29 ± 0.28	8.33 ± 4.20	1.70 ± 0.16	2.03 ± 0.36
Daily sperm production/testis (10^6/testis/day)							
F0	31.65 ± 1.57	31.35 ± 1.87	34.35 ± 1.52	31.94 ± 1.43	31.10 ± 1.85	35.59 ± 1.44	32.90 ± 1.30
F1	46.19 ± 2.70	45.33 ± 2.55	42.78 ± 2.12	45.51 ± 2.80	44.42 ± 2.16	44.95 ± 1.64	44.67 ± 2.79
F2	37.15 ± 2.12	32.30 ± 2.50	36.17 ± 2.24	36.14 ± 2.62	36.61 ± 1.85	32.58 ± 2.06	33.00 ± 2.41
F3	34.84 ± 1.71	30.27 ± 1.23	30.66 ± 0.94	32.07 ± 1.35	30.63 ± 1.35	31.87 ± 1.63	28.21 ± 1.20**
Efficiency of daily sperm production (10^6/g testis/day)							
F0	18.28 ± 0.76	17.91 ± 0.94	20.02 ± 0.92	18.39 ± 0.75	18.07 ± 1.03	20.74 ± 0.85	19.14 ± 0.74
F1	24.91 ± 1.41	26.89 ± 1.46	24.18 ± 1.21	25.05 ± 1.40	24.77 ± 1.08	25.44 ± 1.01	27.51 ± 1.67
F2	19.93 ± 1.15	17.64 ± 1.34	20.67 ± 1.32	19.60 ± 1.35	20.17 ± 1.17	18.86 ± 1.24	20.05 ± 1.30
F3	19.16 ± 0.92	18.28 ± 0.84	18.20 ± 0.51	18.28 ± 0.69	17.83 ± 0.64	19.26 ± 0.96	17.56 ± 0.71

Note. Additional parameters evaluated included mating and fertility indices for both sexes, gestational index, number dead pups on postnatal day (PND) 0, stillbirth index, and live birth index for females and testicular homogenization-resistant spermatid head concentration for males (data not shown).

*$p < 0.05$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM.

**$p < 0.01$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM.

***$p < 0.001$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM.

secondary to the decreased body weights. The difference in effects on weanling versus adult animals is likely the result of the very high dietary intakes (greater than 750 [786–1205] mg/kg/day) of the test material being consumed by the weanling animals in the high dose group (in their first postwean exposure week). These intakes are approximately 1.5 to 2 times

TABLE 6
Summary of Selected F1, F2, and F3 Offspring Reproductive Developmental Parameters

Parameter	Generation	BPA dietary concentration (ppm) 0	0.015	0.3	4.5	75	750	7500
Males and females								
No live pups/litter (PND 0)	F1	14.3 ± 0.6	14.7 ± 0.7	14.1 ± 0.5	13.3 ± 0.6	13.7 ± 0.5	12.9 ± 0.6	11.5 ± 0.4**
	F2	14.6 ± 0.6	14.9 ± 0.4	14.3 ± 0.7	14.7 ± 0.7	14.3 ± 0.4	14.9 ± 0.5	10.8 ± 0.5***
	F3	14.8 ± 0.4	14.1 ± 0.4	13.2 ± 0.5*	13.6 ± 0.6	13.9 ± 0.4	13.7 ± 0.4	10.9 ± 0.4***
4 Day survival index (no surviving 4 days/no live on PND 0)	F1	95.2 ± 3.8	98.1 ± 0.6	99.4 ± 0.4	98.9 ± 0.7	99.8 ± 0.2	98.2 ± 0.9	99.0 ± 0.7
	F2	98.6 ± 0.5	99.2 ± 0.4	95.6 ± 1.4	98.6 ± 0.6	98.9 ± 0.5	99.6 ± 0.3	93.9 ± 3.7
	F3	96.1 ± 1.4	98.0 ± 1.0	94.5 ± 3.4	98.3 ± 0.6	98.4 ± 0.8	97.6 ± 0.9	99.1 ± 0.5
Lactational index (no surviving 21 days/no live postcull on PND 4)	F1	99.6 ± 0.4	99.6 ± 0.4	100.0 ± 0.0	99.6 ± 0.4	100.0 ± 0.0	99.6 ± 0.4	97.8 ± 1.3
	F2	99.3 ± 0.5	99.7 ± 0.3	99.7 ± 0.3	99.6 ± 0.4	97.8 ± 1.5	100.0 ± 0.0	99.1 ± 0.7
	F3	99.3 ± 0.5	98.6 ± 0.8	98.9 ± 0.8	100.0 ± 0.0	98.6 ± 0.8	99.6 ± 0.4	98.8 ± 0.8
Females								
AGD (mm)	F2	0.95 ± 0.01	0.98 ± 0.01*	0.98 ± 0.01**	0.98 ± 0.01*	0.97 ± 0.01	0.99 ± 0.01**	0.96 ± 0.01
	F3	0.92 ± 0.02	0.96 ± 0.02	0.91 ± 0.02	0.93 ± 0.02	0.95 ± 0.01	0.95 ± 0.01	0.94 ± 0.01
Body weight/litter PND 0 (g)	F1	6.19 ± 0.12	6.10 ± 0.12	6.29 ± 0.12	6.17 ± 0.10	6.27 ± 0.12	6.18 ± 0.18	6.00 ± 0.09
	F2	5.97 ± 0.11	6.10 ± 0.09	5.94 ± 0.15	6.13 ± 0.08	6.01 ± 0.12	6.00 ± 0.08	5.99 ± 0.10
	F3	5.98 ± 0.09	6.34 ± 0.10	6.14 ± 0.08	6.31 ± 0.15	5.99 ± 0.09	6.10 ± 0.13	6.14 ± 0.07
Absolute age at VP (days)	F1	30.5 ± 0.3	30.7 ± 0.4	30.2 ± 0.2	30.6 ± 0.3	30.1 ± 0.3	31.0 ± 0.3	33.0 ± 0.6***
	F2	31.0 ± 0.3	31.2 ± 0.4	31.2 ± 0.4	33.5 ± 2.2	32.1 ± 0.4*	31.9 ± 0.4	34.5 ± 0.5***
	F3	31.3 ± 0.3	31.1 ± 0.3	31.1 ± 0.3	31.1 ± 0.5	31.6 ± 0.3	30.9 ± 0.3	33.8 ± 0.5***
Age at VP (days) adjusted for body weight at acquisition	F1	30.3 ± 0.3	30.1 ± 0.3	30.4 ± 0.3	30.1 ± 0.3	30.3 ± 0.3	30.9 ± 0.3	33.9 ± 0.3***
	F2	31.3 ± 0.4	31.2 ± 0.4	31.7 ± 0.4	31.8 ± 0.4	31.9 ± 0.4	32.2 ± 0.4	35.3 ± 0.4***
	F3	31.1 ± 0.3	30.8 ± 0.3	31.3 ± 0.3	30.9 ± 0.3	31.4 ± 0.3	31.1 ± 0.3	34.3 ± 0.3***
Age at VP adjusted for body weight on SD 7 (days)	F1	30.6 ± 0.3	30.8 ± 0.3	30.2 ± 0.3	30.6 ± 0.3	30.2 ± 0.3	31.0 ± 0.3	32.5 ± 0.4***
	F2	31.1 ± 1.0	31.3 ± 0.9	31.2 ± 0.9	33.6 ± 0.9	32.2 ± 0.9	31.9 ± 0.9	34.1 ± 1.1
	F3	31.2 ± 0.4	30.9 ± 0.4	31.1 ± 0.4	31.0 ± 0.4	31.6 ± 0.4	30.9 ± 0.4	34.1 ± 0.4***
Body weight at acquisition (g)	F1	102.52 ± 2.08	105.51 ± 2.10	98.98 ± 1.41	106.04 ± 2.60	99.71 ± 1.50	102.27 ± 1.79	92.32 ± 2.54**
	F2	105.04 ± 1.97	106.47 ± 2.50	104.23 ± 2.29	114.63 ± 8.94	107.46 ± 2.06	105.14 ± 2.34	102.50 ± 2.89
	F3	105.59 ± 2.38	106.30 ± 2.48	101.85 ± 2.23	105.64 ± 2.85	105.15 ± 1.98	102.41 ± 1.86	99.04 ± 2.48
Males								
AGD (mm)	F2	1.98 ± 0.01	2.00 ± 0.02	1.98 ± 0.02	1.97 ± 0.01	1.95 ± 0.01	1.96 ± 0.02	2.00 ± 0.01
	F3	1.97 ± 0.02	1.97 ± 0.02	1.97 ± 0.04	2.00 ± 0.03	2.01 ± 0.02	2.00 ± 0.02	1.96 ± 0.02
Body weight/litter PND 0 (g)	F1	6.53 ± 0.11	6.36 ± 0.14	6.69 ± 0.12	6.60 ± 0.10	6.62 ± 0.12	6.49 ± 0.17	6.37 ± 0.11
	F2	6.28 ± 0.11	6.51 ± 0.11	6.28 ± 0.16	6.45 ± 0.08	6.40 ± 0.12	6.42 ± 0.10	6.38 ± 0.10
	F3	6.36 ± 0.10	6.71 ± 0.10	6.51 ± 0.08	6.66 ± 0.15	6.40 ± 0.10	6.49 ± 0.12	6.49 ± 0.08
No nipples/male pup (PND 11-13)	F1	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	F2	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	F3	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
No areolae/pup (PND 11-13)	F1	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.06 ± 0.04	0.04 ± 0.03	0.01 ± 0.01
	F2	0.05 ± 0.03	0.06 ± 0.03	0.09 ± 0.06	0.04 ± 0.03	0.02 ± 0.01	0.05 ± 0.03	0.05 ± 0.03
	F3	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.06 ± 0.03	0.03 ± 0.02	0.00 ± 0.00
Absolute age at PPS (days)	F1	41.9 ± 0.3	43.2 ± 0.4	43.1 ± 0.3	42.2 ± 0.3	42.8 ± 0.4	43.6 ± 0.4**	45.8 ± 0.3***
	F2	42.1 ± 0.3	43.5 ± 0.3	43.7 ± 0.4**	42.9 ± 0.3	43.3 ± 0.3**	43.2 ± 0.3*	47.9 ± 1.8***
	F3	42.1 ± 0.4	42.2 ± 0.3	43.1 ± 0.4	41.9 ± 0.4	42.8 ± 0.3	43.1 ± 0.2	45.2 ± 0.4***
Age at PPS adjusted for body weight at acquisition (days)	F1	41.9 ± 0.3	42.8 ± 0.3	42.7 ± 0.3	42.0 ± 0.3	42.7 ± 0.3	43.6 ± 0.3**	46.8 ± 0.4***
	F2	41.9 ± 0.6	41.6 ± 0.7	43.2 ± 0.6	42.9 ± 0.6	43.1 ± 0.6	43.8 ± 0.6	49.3 ± 0.7***
	F3	42.0 ± 0.3	42.0 ± 0.3	43.1 ± 0.3	41.9 ± 0.3	42.6 ± 0.3	43.0 ± 0.3	46.0 ± 0.4***
Age at PPS adjusted for body weight on SD 14 (days)	F1	42.0 ± 0.3	43.3 ± 0.3	43.3 ± 0.4	42.4 ± 0.3	42.8 ± 0.3	43.6 ± 0.3*	45.2 ± 0.4***
	F2	42.5 ± 0.7	43.0 ± 0.7	43.9 ± 0.7	43.0 ± 0.7	43.3 ± 0.7	43.1 ± 0.7	46.7 ± 0.8**
	F3	42.1 ± 0.3	42.3 ± 0.3	43.1 ± 0.4	42.0 ± 0.3	42.8 ± 0.3	43.1 ± 0.3	45.0 ± 0.4***
Body weight at acquisition (g)	F1	215.70 ± 3.10	221.28 ± 3.42	225.06 ± 2.72	220.57 ± 3.56	216.69 ± 2.98	214.19 ± 3.82	194.02 ± 3.33***
	F2	219.74 ± 3.76	228.70 ± 3.34	223.26 ± 3.97	217.31 ± 3.20	219.83 ± 2.93	211.36 ± 3.63	200.13 ± 5.28**
	F3	209.33 ± 3.39	214.40 ± 3.26	208.32 ± 4.05	208.37 ± 3.37	214.31 ± 3.48	210.46 ± 3.34	186.76 ± 2.59***

Note Additional parameters evaluated included number of live pups per litter on postnatal day (PND) 4, 7 and 14, survival indices for PND 4-7, 7-14 and 14-21 and percent male pups with 1 or more nipples/areolae (data not shown)

*$p < 0.05$, as compared to control values using appropriate statistical methods data presented as mean ± SEM

**$p < 0.01$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM

***$p < 0.001$, as compared to control values using appropriate statistical methods, data presented as mean ± SEM

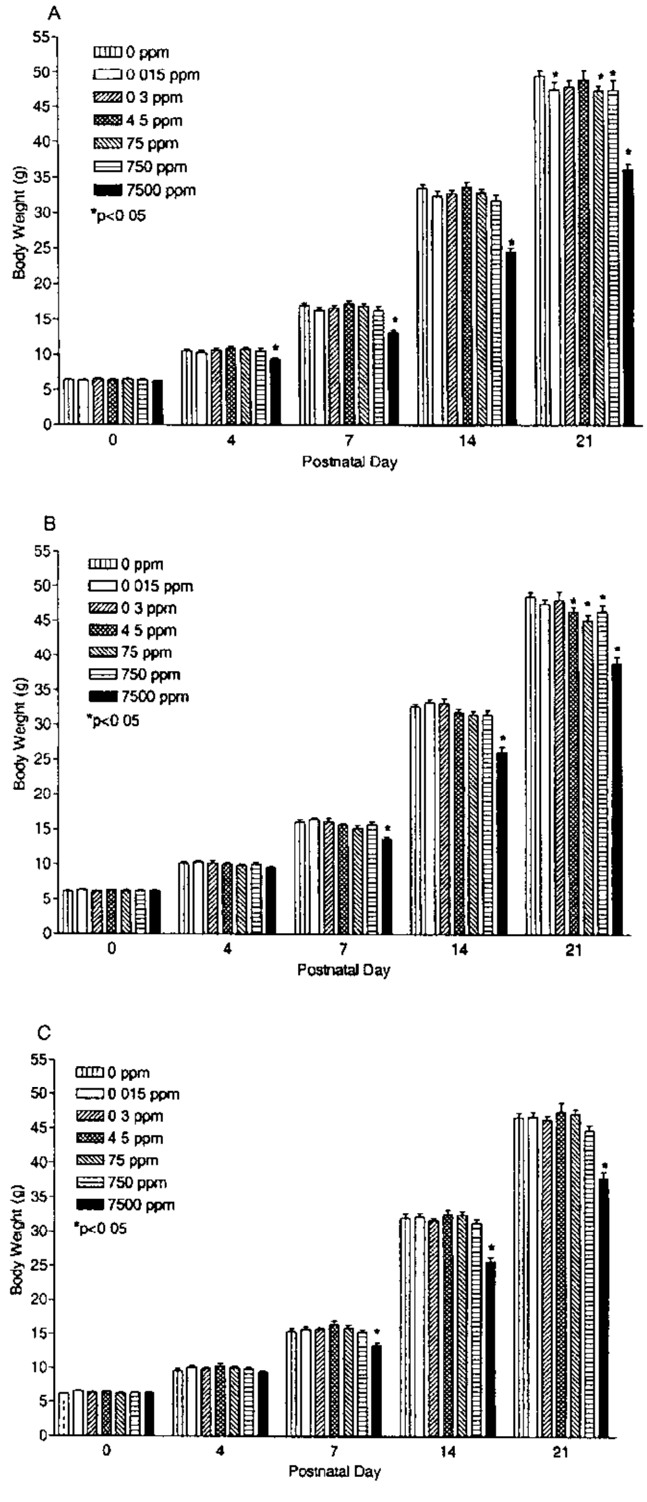

FIG 5 Offspring body weights during lactation Data are presented for sexes combined as mean grams per litter ± SEM Note for F1 pups on PND 4, body weight was significantly reduced at 7500 ppm when sexes were combined, but not when sexes were analyzed separately (A) F1 pups, (B) F2 pups, and (C) F3 pups

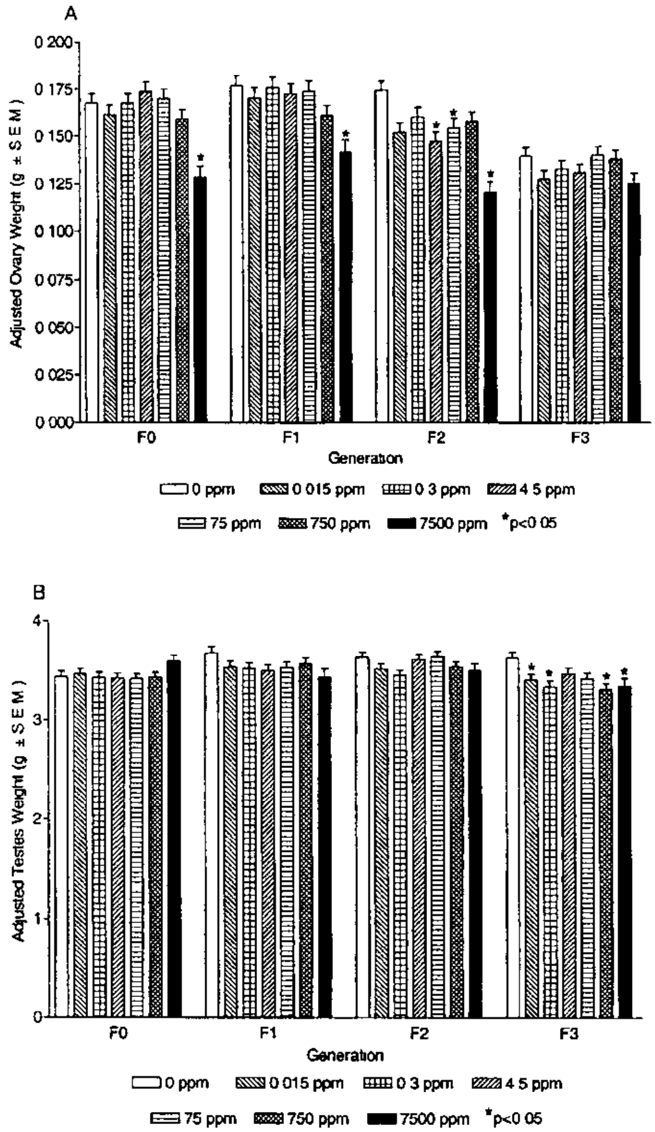

FIG 6 Average gonad weight covaried by body weight at necropsy Data are presented as mean weight in g ± SEM (A) Ovary weight for F0, F1, F2, and F3 females (B) Testes weight for F0, F1, F2, and F3 males

the daily intakes in the adults at the same dose (less than 575 [534–570] mg/kg/day, during the last prebreed exposure week immediately prior to mating) BPA intakes in Table 1 and for F1 postwean males and females in Figures 3B, 3D, and 4 indicate that the maximum exposure to BPA, in mg/kg/day for all animals during all phases of the study, was during the first week of prebreed for the pups (when they were small and in a growth spurt) and the last week of lactation for the dams (where there could have been a substantial contribution from pups self feeding)

Total and live pups per litter Also, only at 7500 ppm were there reduced total and live litter sizes on PND 0. The explanation for the reduced number of total and live pups per litter at birth at 7500 ppm for F1, F2, and F3 offspring is not known It is not due to effects on males, since there is no evidence of reproductive effects on the males at 7500 ppm (or any other dietary dose) It is not due to prenatal postimplantation loss of conceptuses, since postimplantation loss was not affected at any dose for F0, F1, and F2 dams carrying F1, F2, and F3 litters Preimplantation loss cannot be determined from this study design, since by the time the parental females are sacrificed (at the weaning of their litters), the ovarian corpora lutea of pregnancy (which form after ovulation) have involuted to corpora albicans, indistinguishable from corpora albicans from previous ovulation cycles The possibilities, therefore, exist that there were increased preimplantation loss and/or fewer eggs ovulated at 7500 ppm Although the absolute and relative paired ovarian weights were reduced in F0, F1, F2, and F3 (absolute only) females in this study, there was no evidence of reduced ovarian primordial follicle counts at 7500 ppm in any generation

Biegel *et al* (1998a) also reported reduced live litter sizes associated with reduced number of implantations per litter (the latter was not observed in the present study) at 2 5 ppm dietary E2, but did not offer an explanation In the present study, dams at 7500 ppm exhibited profound reductions in body weight and weight gain, which is at least consistent with effects of profound maternal systemic toxicity as causative per se

Acquisition of Pubertal Characteristics

VP and PPS Reduced body weights are also most likely the cause of the significant delay in acquisition of puberty in both sexes (age at acquisition of VP in females and PPS in males), observed in all offspring generations at 7500 ppm, using ANCOVA with body weight at acquisition as the covariate Analysis of the ages at acquisition alone (by nonparametric Kruskal-Wallis and Mann-Whitney U tests) did result in significant delays at lower doses (rarely and not consistently), but the values were not significant with ANCOVA (Fig 7)

Body weight at acquisition was significantly reduced at 7500 ppm for F1 males and females and for F2 and F3 males with ANCOVA However, acquisition of developmental landmarks is dependent on both age and weights, i e , heavier animals acquire the landmark earlier, while lighter animals acquire the landmark later However, lighter animals do eventually acquire the landmark (unless there is another cause for the delay) and in many cases acquire the landmark at the same or lighter weight than the heavier animals, but at an older age (e g , Carney *et al*, 1998, Kennedy and Mitra, 1963) All animals in this study acquired puberty The lighter animals acquired puberty at a later time (older age) Most of them were comparable in weight at the time of acquisition to the control (and lower dose groups) animals that acquired puberty at an earlier time (and thus, a younger age)

There is much discussion among reproductive toxicologists

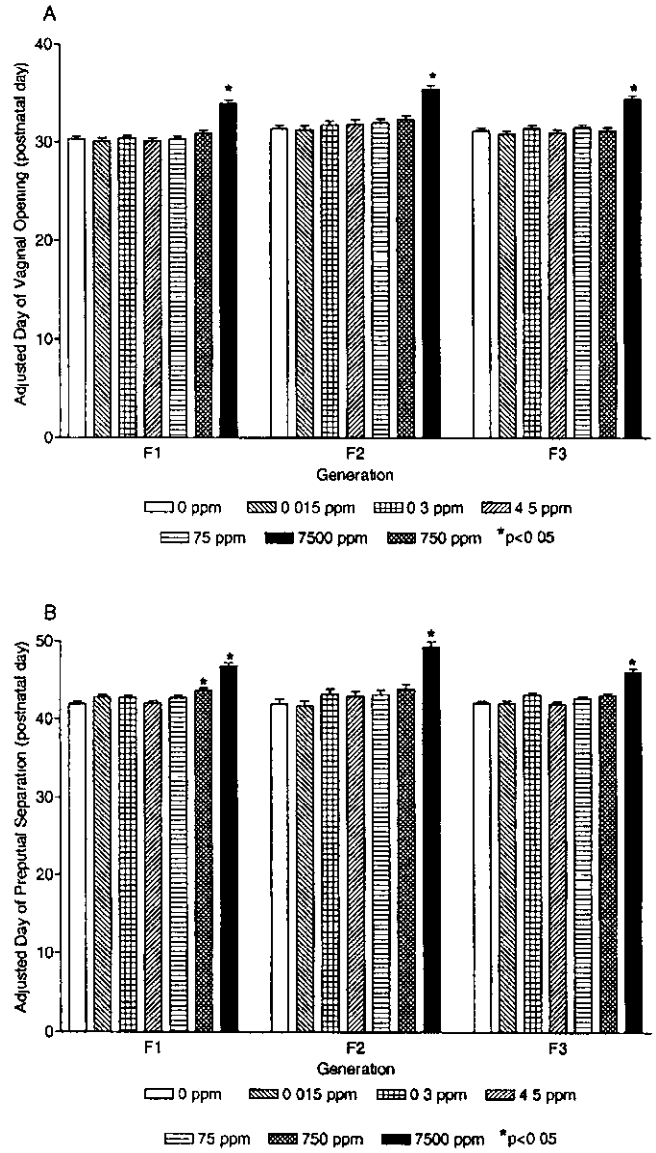

FIG 7 Mean age at acquisition of puberty covaried by body weight at day of acquisition Data are presented as adjusted age in postnatal days ± SEM (A) Vaginal patency (VP) for F1, F2, and F3 females (B) Preputial separation (PPS) for F1, F2, and F3 males

as to the most appropriate body weight to use as a covariate for ANCOVA other than that at acquisition. We covaried age at acquisition of puberty both by the body weight at acquisition (to standardize pup weights to the same physiologic state, i e , puberty regardless of age) and by the body weight on a prebreed study day, encompassing the time of acquisition (i e , SD 7 for females and SD 14 for males) to standardize pup weights to the same age, regardless of physiologic state

To use the body weights on SD 7 and 14 as the covariate for age at acquisition of puberty, we established that the ages for each group on the chosen study day, within each generation, were equivalent (by ANOVA), and that the variances (i.e., the distributions) also did not differ (by Levene's test). The results for the covariate analyses by body weight on SD 7 (females) or SD 14 (males) are presented in Table 6. The ANCOVA analyses resulted in essentially the same findings, regardless of which body weight was employed as the covariate, which is consistent with the reduced body weights in both sexes in all 3 offspring generations throughout their respective prebreed periods at 7500 ppm.

Since acquisition of both landmarks in both sexes of both generations was delayed, these results are probably not caused by estrogen receptor-mediated events or other endocrine-related toxicity. The only endocrine-mediated mechanism currently known to result in delays in puberty in both sexes would be interference with steroidogenesis, thereby reducing testosterone (and DHT) levels in males and estrogen levels in females, and there is no evidence that BPA interferes with steroidogenesis in rats. It is most likely that the delays in puberty in both sexes at 7500 ppm were caused by reduced body weights prior to and at acquisition in all offspring generations.

This interpretation is consistent with the recognition by the U.S. EPA (1996, p. 56295) that "body weight at puberty may provide a means to separate specific delays in puberty from those that are related to general delays in development." The delays in VP in females and in PPS in males at 7500 ppm in this study were relatively minor: 2.5 (F1, F3) and 3.5 (F2) days for females and 3.1 (F3), 3.9 (F1), and 5.8 (F2) days for males (the delay in acquisition in F1 males at 750 ppm was 1.7 days). Biegel *et al.* (1998a,b) have shown that dietary administration of E2 at 0.05 and 2.5 ppm resulted in accelerated VP (by 7 days) in CD (SD) rats.

AGD. The significant effect on acquisition of reproductive landmarks in F1 and F2 offspring required a measurement of AGD in newborn F2 and F3 offspring, as specified in the guidelines (U.S. EPA, 1998). AGDs in newborn F2 and F3 males were statistically equivalent across all groups at PND 0. In the newborn F2 females, AGD was statistically significantly longer at 0.015, 0.3, 4.5 (not 75), and 750 (not 7500) ppm, with mean values of 0.98, 0.98, 0.98, and 0.99 mm, respectively, relative to the control group mean value of 0.95 mm (and 0.97 mm at 75 ppm and 0.96 mm at 7500 ppm, Figs. 8A and 8B). These effects were increases in AGD of only 0.03–0.04 mm, equivalent to increases of only 3.16–4.21%. They were also present only at doses where the mean F2 female body weights per litter were slightly, but not statistically significantly, higher than in the control group and in the groups with unaffected AGDs; body weights, per se, are known to affect AGD (Gallavan *et al.*, 1999). These small differences (0.03–0.04 mm), especially since the AGDs for F3 female pups in all groups were statistically equivalent, are considered of no biological significance because the magnitude of the differences is minimal, all mean values round to 1.0 mm, and these changes,

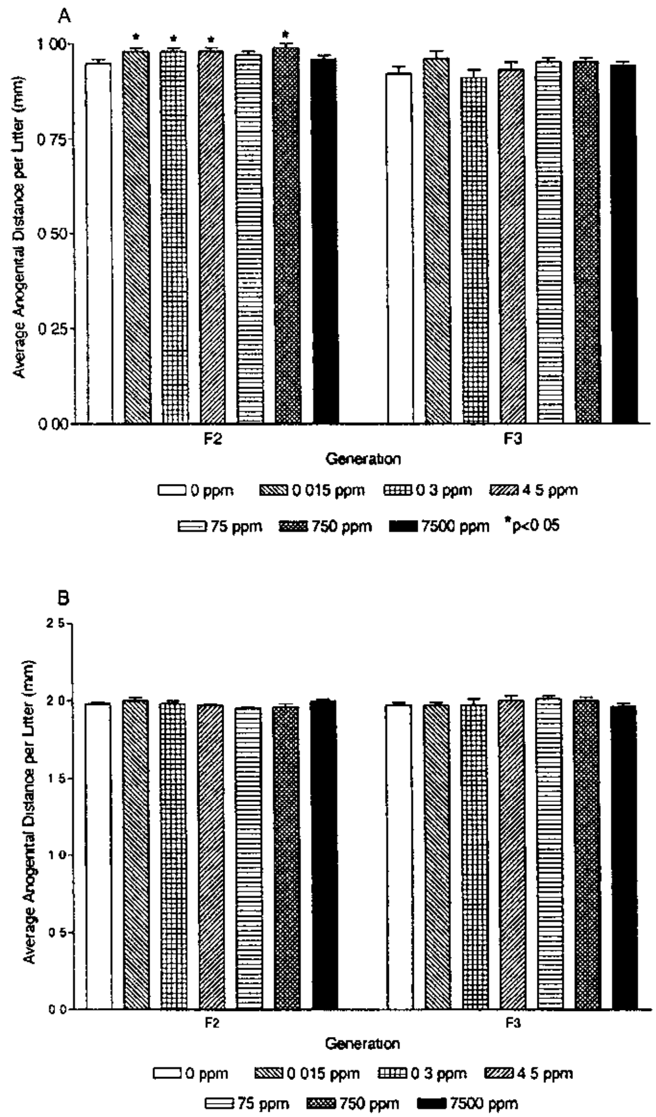

FIG. 8. Average anogenital distance (AGD) on PND 0. Data are presented as mean distance in mm ± SEM. (A) F2 and F3 females, (B) F2 and F3 males.

along with the similarly minor delays in acquisition of PPS and VP, are not associated with any alterations in reproductive organ structures or function in the animals exhibiting them. In addition, AGD is under androgenic control, specifically dihydrotestosterone (Gray *et al.*, 1998; Gray and Ostby, 1998) and is not affected by estrogens (Biegel *et al.*, 1998a). BPA was shown to be neither an androgen nor antiandrogen *in vivo* (Laudenbach *et al.*, 2001). Therefore, the effects reported on F2 female AGD are considered of no biological significance and not due to BPA exposure.

Comparisons across Generations

One of the possible analyses that can be done with a multigeneration dataset is to characterize an effect (or lack thereof) across generations This is permitted if 2 important statistical criteria are met the control groups are not statistically different and there is no interaction between dose and generation, i e , a dose × generation interaction

To determine if it was appropriate for data across generations to be pooled, a two-way ANOVA was performed for organ weights (such as epididymides, testis, and ovaries), developmental landmarks (VP and PPS), and AGD The results showed that several parameters could be pooled and several could not be pooled For testis and epididymides weights, there were significant differences between F1 and F3 controls (p = 0 0004) and between F2 and F3 controls (p = 0 0001), respectively This is understandable since the F3 animals were younger, had less total exposure duration to BPA, and had never been mated

For daily sperm production, there were significant differences between the F1 controls and both F2 (p = 0 0048) and F3 (p = 0 0005) controls This was understandable since the F1 generation controls had a lower epididymal sperm concentration but a higher spermatid head concentration than the other generations, which caused the DSP and efficiency of daily sperm production to be higher than the other generations For ovary weight, the results (p = 0 0007) of the ANOVA for interaction showed that there was a significant dose × generation effect Based on these results, the generations could not be pooled for epididymides, testis, or ovary weights or for DSP Thus, the only statistically valid comparisons for these parameters were between doses for each individual generation and its concomitant control

For PPS, VP, and AGD for both males and females, there were no statistical differences among control groups (for PPS, p = 0 8797, for VP, p = 0 1848, for AGD male, p = 0.7262, for AGD female, p = 0 3181) This is also understandable since the animals were all covaried with body weight at the same study day (SD 7 for females and SD 14 for males), were statistically the same age on that date (no statistical differences in the distribution of ages among groups), and had the same range of total exposure durations to BPA across groups Thus, the data for these 3 parameters could be pooled.

The pooled data (n = 385 litters, dose and dose × generation df = 6) from both F2 and F3 generations for male AGD showed the same results as did the individual generations when compared to their concomitant controls (i e , there were no effects of BPA at any dose in any generation or across generations) For pooled female AGD (n = 385 litters, dose and dose × generation df = 6), none of the values differed more than 0 04 mm from the control value, although 3 were statistically significant (at 0 3, 750, and 7500 ppm) None of the individual values for female AGD for the F3 generation differed more than 0 04 mm from the control value (as with the pooled values), and none of these 6 dose group values were statistically different from its concomitant control value None of the F2 values differed more than 0 04 mm from the control values, yet 4 of the 6 doses were statistically significant Biologically, the difference of 0.04 mm is insignificant and most likely due to the exceptionally well-controlled micrometric measurement techniques for AGD (all standard errors were within 0 02 mm of the mean)

The pooling (n = 626, dose and dose × generation df = 6) of the PPS data across all 3 offspring generations created a statistically significant difference at 0.3 ppm, which was not present in any of the individual generations No other dose below 750 ppm in any generation or in the pooled data was significant. Thus, this finding was considered to be an anomaly and not biologically meaningful

The pooled data (n = 627, dose and dose × generation df = 6) from all 3 offspring generations for VP showed the same results as the data from the individual generations when compared to their concomitant controls, i e , there were no effects of BPA at any dose in any generation or across generations other than at the highest dose of 7500 ppm

Based on the results of the statistical tests for the pooled data, pooling the data did not lend any more insight into interpretation of the data than did just comparing individual generations with their concomitant controls

Other Research and Routes of Exposure in Rat Reproductive Toxicity Evaluations

Absence of effects Welsch and colleagues (Elswick *et al*, 2000, Welsch *et al*, 2000, 2001) reported that exposure of CD (SD) female rats (13–16 pregnancies/group) to BPA in drinking water at 0, 0 005, 0 5, 5, or 50 mg/l from GD 2 through PND 21 (with intakes of ~ 0 001 to ~ 10 mg/kg/day) resulted in no effects on differentiation and function of the reproductive system in female (Welsch *et al*, 2000) or male (Elswick *et al*, 2000) F1 offspring when evaluated through 10 months of age In F1 females, there were no effects of BPA on fertility, fecundity, organ weights, AGD, VP, age at first estrus, estrous cyclicity, ovarian follicle counts, or lordosis The positive control DES (at 0 05 mg/l) did cause accelerated VP and age at first estrus in females In F1 males, there were no effects of BPA on AGD, PPS, organ weights, hormone levels, sperm counts, fertility, immunohistochemically measured ventral prostate AR levels, and no treatment-related histopathological changes

Other researchers have also reported no effect of exposure to BPA at low doses Kwon *et al* (2000) administered BPA by gavage to pregnant CD (SD) rats at 0, 3.2, 32, or 320 mg/kg/day from GD 11 through PND 20 DES at 15 μg/kg/day was employed as a positive control Offspring female pubertal development was unaffected by indirect BPA exposure at any dose There were also no effects on the volume of the sexually dimorphic nucleus of the preoptic area (SDN-POA) of the brain in 10-day-old offspring females, on estrous cyclicity, on sexual behavior of the offspring females at 4 months of age, or on offspring male reproductive organ weights at 6 months of age (including testis, epididymis, seminal vesicle, and ventral and dorsolateral prostate lobes). DES increased the volume of the SDN-POA in offspring females and caused irregular estrous cyclicity.

Ema *et al.* (2001) from the Chemical Compound Safety Research Institute in Hokkaido, Japan, administered BPA in distilled water by gavage (stomach tube) to Crj CD (SD) rats, 25/sex/dose at 0, 0.2, 2, 20, and 200 μg/kg/day. This study, like the present study, was conducted under GLP regulations and was compliant with the U.S. EPA testing guidelines (U.S. EPA, OPPTS, 837.3800, 1998). The Ema study also included endocrine-sensitive measurements and neurobehavioral endpoints, evaluating functional development in F1 and F2 offspring (open field motor activity and Morris water maze learning and memory tests), and various serum hormone concentrations in F0 and F1 parental animals and retention of F2 weanlings. Thirty-seven animals per sex per group (25 from the main study and 12 from "satellite groups") were evaluated until adulthood, including gross necropsy, organ weights, and histopathology for F2 males and estrous cyclicity and gross necropsy for F2 females. The authors concluded that "oral doses of BPA of between 0.2 and 200 μg/kg administered over two generations did not cause significant compound-related changes in reproductive or developmental parameters in rats" (Ema *et al.*, 2001, p. 522). These conclusions are supported by our findings of no biologically relevant effects of BPA below 5 mg/kg/day in any generation in either sex.

Nagao *et al.* (1999) administered BPA by sc injection to rat pups on PND 1–5 at 300 μg/g (300 mg/kg/day) and reported no effects on male or female reproductive development or on adult offspring reproductive structures or functions. Estradiol benzoate was also administered by the same route and timing to a separate group and caused clear effects in male and female reproductive development and in reproductive structures and functions.

Atanassova *et al.* (2000) and Williams *et al.* (2001) showed that Wistar rats treated neonatally with a range of doses (0.01–10 μg, equivalent to 1.0 μg–1.0 mg/kg in a 10-g neonatal rat pup) of DES on alternate days from PND 2 to 12 developed a dose-dependent retardation of pubertal spermatogenesis on day 18, as evidenced by decreases in testis weight, seminiferous tubule lumen formation, spermatocyte nuclear volume per unit Sertoli cell, and elevation of the germ cell apoptotic index. The 2 lowest doses of DES (0.1 and 0.01 μg) significantly increased spermatocyte nuclear volume per unit Sertoli cell. Similarly, daily treatment on PND 2–12 with BPA (0.5 mg, equivalent to 50 mg/kg in a 10 g neonatal rat pup) significantly advanced this and some of the other aspects of pubertal spermatogenesis. In adulthood, testis weight was decreased dose dependently in rats treated neonatally with DES, but only the lowest dose group (0.01 μg) showed evidence of mating (3 of 6) and normal fertility (3 litters). Animals treated neonatally with BPA had increased testis weights and exhibited "reasonably normal" mating/fertility (Attanassova *et al.*, 2000, pp. 3898 and 3904). The authors concluded that the effect of high doses of BPA on the first wave of spermatogenesis at puberty was "essentially benign" (Attanassova *et al.*, 2000, pp. 3898 and 3908). Furthermore, this group concluded that weak environmental estrogens in general are "unlikely to pose a significant risk to the reproductive system of the developing human male unless the compound in question also possesses some other biological activity of relevance" (Williams *et al.*, 2001, p. 245).

Rubin *et al.* (2001) reported no effects on the number of pups per litter, sex ratio, day of VP, AGD, and no significant histopathological findings in offspring of rats (SD) exposed to BPA in drinking water to approximately 0.1 and 1.2 mg/kg/day from GD 6 through lactation. Kubo *et al.* (2001) showed that a BPA dose of 1.5 mg/kg/day in drinking water to 10 female Wistar rats during pregnancy and lactation produced no differences between organ weights (testis, epididymis, ventral prostate, ovaries, uterus) and serum hormone levels (LH, FSH, testosterone, or 17β-estradiol) in offspring at 12 weeks of age, when compared to the control group values. Ramos *et al.* (2001) reported no effects on litter size, male or female pup body weight, sex ratios, or AGD following exposure to 25 μg/kg/day and 250 μg/kg/day of BPA dissolved in DMSO administered by continuous sc infusion via osmotic pump from GD 8 to PND 23 to pregnant Wistar rats (4 dams/group).

The data presented above from other laboratories for BPA administered by various routes of exposure are consistent with the findings from the present study, which indicated no effects of BPA at 0.001–5 mg/kg/day (i.e., at low doses) when administered in the feed.

Presence of effects. Still others have reported effects of BPA exposure in rats, usually by some nonstandard means of dose delivery, such as via continuous sc infusion by implanted osmotic minipumps or at relatively high doses. Steinmetz *et al.* (1997) exposed Fischer (F344) and SD rats to BPA (approximate dose of 220–225 μg/kg/day) or E2 (approximate dose of 6–7.5 μg/kg/day), using silastic implants for 3 days. With BPA, F344 rats showed an increase in serum prolactin levels and hyperprolactinemia but showed no effect on anterior pituitary weight. There were no effects on either endpoint with the SD rat. E2 produced hyperprolactinemia in both strains of rat, but produced an increase in anterior pituitary weight in only the F344 rat. Stoker *et al.* (1999) reported that BPA, given to male (prepubertal) Wistar rat pups on PND 22–32 by sc injections of 0 or 50 mg/kg once daily, stimulated increased secretion of prolactin during the dosing period and increased mean lateral prostate weight and inflammation of the lateral lobes of the prostate at 120 days of age. Tohei *et al.* (2001) also reported increased serum prolactin and increased plasma concentrations of luteinizing hormone in male Wistar rats exposed to 1 mg/kg BPA via sc injection for 2 weeks.

Chahoud and his colleagues (Fialkowski and Chahoud, 2000; Schönfelder *et al.*, 2001; Talsness and Chahoud, 2000; Wu and Chahoud, 2000) exposed pregnant SD rats to BPA by gavage on GD 6–21 at doses of 0, 0 02, 0 1, and 50 mg/kg (11-20 litters/group) and reported various effects of sexual development in the offspring However, the NTP Environmental Disrupters Low-Dose Peer Review Statistics Subpanel indicated that a "severe design deficiency" of absence of a concurrent control group precluded "statistical reanalysis of the data" [and] "any reliable assessment of the effects" reported for BPA by this group (NTP, 2001, Appendix A, p A-58)

Rubin *et al* (2001) reported increased body weight gain in offspring of SD rats exposed to BPA in drinking water to approximately 0 1 and 1 2 mg/kg/day from GD 6 through lactation They also reported altered patterns of estrous cyclicity and lowered plasma LH levels in the high-dose BPA group Kubo *et al* (2001) showed that a BPA dose of 1 5 mg/kg/day in drinking water to 10 female Wistar rats during pregnancy and lactation produced similar results at weeks 6 and 7 in offspring (5/sex/litter) for movement, passive avoidance patterns, and size of the locus coeruleus (7 rats total/sex for BPA, 6 rats/sex for control at week 20) In the control group, females showed a higher activity, lower avoidance memory, and larger locus coeruleus than the males

Ramos *et al* (2001) reported that both 25 μg/kg/day and 250 μg/kg/day of BPA, dissolved in DMSO administered by continuous sc infusion via osmotic pump from GD 8 to PND 23 to pregnant Wistar rats (4 dams/group), produced an effect on the proliferation and differentiation of epithelial and stromal cells in the ventral prostate (up to 4 rats/litter) This was expressed as an increase in the fibroblast smooth muscle cell ratios and a decrease in the AR-positive cells of the periductal stroma

Takahashi and Oishi (2001) reported that young (4 weeks of age) F344 rats (8/group), given dietary concentrations of 0, 234, 466, and 950 mg/kg/day of BPA for 44 days, had decreased body weight, food consumption, and liver weight at 466 and 950 mg/kg/day and increased kidney weight at all 3 doses Seminal vesicle and dorsolateral prostate gland weights were decreased at only 950 mg/kg/day, and seminal vesicle weight was decreased at all BPA doses Although there were no effects on testis, epididymides, or ventral prostate gland weight at any BPA dose, histopathological examination of the testes revealed seminiferous tubule degeneration and loss of elongated spermatid in a dose-dependent fashion at all doses.

Many of the effects observed by the above authors were from BPA administered by various parenteral (non-oral) routes, versus the present study with BPA administered in the diet, or were endpoints not directly evaluated in the present study Results from the present study do confirm effects on body and systemic (but not reproductive or accessory sex) organ weights at high doses (750 and 7500 ppm)

Strain Differences

One recent, recurring concern is the possible differential responsiveness of various rat (and mouse) strains to endocrine-active compounds Diel *et al* (2001a) reported that ovariectomized female Wistar, SD, and DaHan rats responded differently in a uterotrophic assay to the oral administration of a positive control, ethinyl estradiol (Wistar = DaHan > SD), and BPA (SD = Wistar > DaHan) after 3 days of dosing. Diel *et al* (2001b) also evaluated the same 3 rat strains for a uterotrophic response to a number of chemicals, and reported "all analyzed rat strains respond with a comparable sensitivity to phyto- and xenoestrogen treatment" (Diel *et al*, 2001b, p 590)

Steinmetz *et al* (1997) reported that a 3-day exposure to BPA, using silastic implants, resulted in increased serum prolactin levels and hyperprolactinemia in F344 but not SD rats

Long *et al* (2001) found no strain differences between ovariectomized F344 and SD rats (four/group) exposed to BPA by a single ip injection at doses of 0 02 to 150 mg/kg In both strains, BPA elevated vascular endothelial growth factor (VEGF) mRNA expression in the vagina and uterus at 37 5 and 150 mg/kg, respectively The anterior pituitary weight was unaffected in either strain E2 produced hyperprolactinemia in both strains, and anterior pituitary weight was increased only in the F344 rat

The Wistar rat has been shown to be sensitive to gestational and lactational exposure to the positive control, DES, in drinking water (Cagen *et al*, 1999b, Sharpe *et al*, 1995) The CD (SD) rat was appropriately sensitive to E2 at low concentrations in the diet in a 1-generation reproduction study (Biegel *et al*, 1998a,b) It appears that the differential sensitivity, if any, of various rat strains depends on the test chemical used and the endpoints evaluated However, the CD (SD) rat appears to be a very good model for detecting endocrine-sensitive effects in a transgenerational study design, especially with a powerful historical control database The performing laboratory has recently confirmed the sensitivity of the CD (SD) rat to dietary E2 and to dietary butylbenzyl phthalate (BBP), an antiandrogen (Tyl, unpublished observations)

Possible explanation of differences in routes of exposure The results of studies that produced effects, even those that did not evaluate reproductive and developmental endpoints or used other strains of rats or other species, can be better understood by considering the qualitatively and quantitatively different responses to different routes of BPA administration Jekat *et al* (2000), Yamasaki *et al* (2000), and Matthews *et al* (2001) showed that oral administration required much higher doses to produce a uterotrophic effect than did sc injection Doses in Jekat *et al* (2000) and Matthews *et al* (2001) ranged from 0 002 to 800 mg/kg for 3 consecutive days in groups of 10 immature Wistar strain-derived rats Indications of estrogenicity were reported at doses of 200 mg/kg/day and above following oral dosing and at doses 20-fold lower (10 mg/kg/day and above) following sc injection Yamasaki *et al* (2000) reported increased uterine weight in SD rats following three consecutive daily BPA doses of 8 mg/kg/day and higher with sc injection, or of 160 mg/kg/day and higher with oral exposure. Kim *et al.* (2001) also reported only weak *in vivo* estrogenic activity in rats following oral administration of 100 mg/kg/day in a similar uterotrophic study design.

Pottenger *et al.* (2000) showed that there was a clear route dependency in the toxicokinetics and metabolism of ^{14}C-labeled BPA after a single oral gavage, ip, or sc dose of either 10 or 100 mg/kg to F344 rats. The relative bioavailability of BPA and the plasma radioactivity were markedly lower after oral administration (C_{max} values were 1 to 2 orders of magnitude lower) as compared to sc or ip administration, thus providing an explanation for the apparent route differences in effects observed for BPA in rats.

Following a single oral dose of 10 mg/kg, greater than 95% of the BPA was immediately glucuronidated in the intestine and the liver and rapidly excreted in the urine (Pottenger *et al.*, 2000). Circulating plasma levels of ^{14}C-BPA (detected by GC/MS) were undetectable at 0.083 h at 10 mg/kg/day and at 0.75 h at 100 mg/kg/day in the male, and after 1 h at 10 mg/kg/day and 18 h at 100 mg/kg/day in the female (limits of quantitation for low and high dose blood samples were 0.01 and 0.1 μg BPA/g blood [10 and 100 ppb], respectively). The major metabolite was confirmed as BPA monoglucuronide (Pottenger *et al.*, 2000), which has been shown to have no estrogenic or antiestrogenic activity (i.e., does not bind to ERα or ERβ) *in vitro* (Matthews *et al.*, 2001; Snyder *et al.*, 2000).

The quantitative differences in effects observed from parenteral versus oral routes of administration, due to the rapid monoglucuronidation of BPA in the intestine and liver after oral administration and the lack of activity of the BPA monoglucuronide, provide an explanation for the results of the present study, i.e., no treatment-related effects at or below 5 mg/kg/day, and systemic toxicity effects only at or above 50 mg/kg/day.

Possible Contributing Factors to Delivered Dose of BPA

Placental transfer. There is limited evidence for placental transfer in rats (Takahashi and Oishi, 2000). BPA at 1000 mg/kg (in propylene glycol), administered by gavage to pregnant F344 rats on GD 18, was rapidly absorbed and distributed into maternal and fetal tissues (maximal concentration 20 min postdosing) and also rapidly cleared. Maternal levels decreased to 2–5% of the maximum by 6 h postdosing (fetal levels were comparably reduced). Relative to the administered dose, the maximum level in maternal blood was 0.007%, 0.083% in liver, and 0.017% in kidney; the maximum level in the fetus was 0.004% of administered dose.

Lactational transfer. There is also limited evidence for lactational transfer in rats (Gould *et al.*, 1998). In a preliminary study, BPA was identified in milk and pups after BPA was administered in the dams' drinking water. A more recent study (Snyder *et al.*, 2000) gave ^{14}C-BPA (ring labeled) at 100 mg/kg by gavage to lactating dams. Radiolabel was detected in the milk, with maximum levels 1 h postdosing (0.95 μg equiv./ml, down to approximately 1/3 of maximal, 0.26 μg equiv./ml, by 26 h). Radiolabel was also detected in pup carcasses beginning at 2 h postdosing, 44.3 μg equiv./kg (with approximately 2× more detected at 24 h, 78.4 μg equiv./kg), i.e., slower uptake and longer retention in the pups. The identity of the radiolabel was BPA monoglucuronide in both the milk and the pups.

Pup self-feeding. During the lactational period, maternal feed consumption is maximal in the rat, but is confounded by pups self-feeding (Cripps and Williams, 1975; Hanley and Watanabe, 1985; Shirley, 1984). At about PND 10, feed can be detected in the stomachs of SD rat pups (Tyl, unpublished observations). Feed is detected in F-344 rat pup stomachs beginning on PND 18 during a 28-day lactation (Hanley and Watanabe, 1985). The size of pups during lactation, relative to that of adult animals, and the data from Hanley and Watanabe (1985), which indicate that during the last week of lactation the pups ingest 38% more feed than the dam on a g/kg basis (140.3/101.5), are consistent with the present authors' estimation that during the last week of lactation (PND 14–21), approximately 30–40% of the feed intake, on a g/kg/day basis (and therefore BPA intake on a mg/kg/day basis), designated as maternal intake is, in fact, pup intake. Test material exposure is therefore significantly underestimated for pups during the last week of lactation and overestimated for dams during this period in F344 (Hanley and Watanabe, 1985) and in CD (SD) rats (Shirley, 1984).

The embryo/fetus and the nursing pup are therefore exposed to BPA/BPA-monoglucuronide during these sensitive life stages from the continuous high dietary BPA exposure to the dam.

Hormonal activity. As noted earlier, BPA has been reported to have weak, estrogen-like activity in some *in vitro* screening assays (Gaido *et al.*, 1997; Krishnan *et al.*, 1993; Kuiper *et al.*, 1997, 1998; Maruyama *et al.*, 1999). Based on the *in vitro* assay results, one might expect BPA to exhibit effects *in vivo* similar to those for the natural estrogen, E2. However, it does not. A comparison of the current study data with a recent 1-generation study with exposure of rats to E2, at concentrations of 0.05, 2.5, 10, and 50 ppm in the diet (Biegel *et al.*, 1998a,b), gave the following results, as presented in Table 7. Except for reduced ovarian weights and reduced F1 offspring litter size at birth in the highest dose in the presence of significant systemic maternal toxicity, BPA did not act like E2.

Assuming comparable pharmacokinetics for BPA and E2, and based on the toxicokinetic information for E2 (*in vitro*: Gaido *et al.*, 1997; *in vivo*: Milligan *et al.*, 1998), the bioavailable fraction for BPA and E2 should be similar at comparable dietary concentrations. BPA is generally reported to be approximately 15,000-fold less potent than E2 from *in vitro* receptor binding/transcriptional activation screening assays (Gaido *et al.*, 1997) and 10,000-fold less potent from *in vivo* sc injection in mice (Milligan *et al.*, 1998). Therefore, it would be expected

TABLE 7
Comparison of Dietary 17β-Estradiol (E2) and BPA on Selected Reproductive Endpoints

Effect	E2 dose	BPA	Comments
Estrous cycle changes (F0)	≥ 0 05	No	—
Total infertility (F0)	≥ 10	No	—
Accelerated (7 days) VP (F1)	≥ 0 05	No	Delayed VP (2 5–3 5 days) for F1, F2, and F3 at 7500 ppm[a]
Delayed (8 days) PPS (F1)	2 5[b]	Yes	Delayed PPS (3 1–5 8 days) for F1, F2, and F3 only at 7500 ppm[a]
Decreased F1 pup weights at birth (Day 0)	≥ 0 05	No	—
Decreased F1 pup weights (Days 4–21)	2 5[b]	Yes	Reduced for PND 7–21 for F1, F2, and F3 only at 7500 ppm[a]
Increased prenatal loss/litter	2 5[b]	No	—
Reduced F1 litter size	2 5[b]	Yes	F1, F2, and F3 at birth only at 7500 ppm[a]
Decreased testes/epididymal/ASG weights (F1)	2 5[b]	No	—
Decreased absolute and relative ovarian weights (F1)	2 5[b]	Yes	F0, F1, F2, F3 (absolute) and F0, F1, F2 (relative) only at 7500 ppm[a]
Reduced number of large antral follicles (F1)	2 5[b]	No	—
Vaginal mucosa thickening (F1)	2 5[b]	No	—

Note E2 data taken from Biegel *et al* (1998a,b) E2 dose is stated in ppm ASG accessory sex gland
[a]Only in the presence of significant systemic maternal toxicity
[b]At doses above 2 5 ppm E2, there was complete infertility (no F1 pups were born)

that BPA doses of 500 ppm or greater (calculated intake of 33 mg/kg/day or greater) should result in effects similar to those described above for E2 at 0 05 ppm or greater However, only 2 of the effects observed for dietary E2 exposure, reduced live litter size at birth and reduced paired ovary weights, were observed in the present study and only at 7500 ppm BPA in the presence of significant maternal systemic toxicity These effects observed for BPA at 7500 ppm may only be related to the significant maternal toxicity that occurred since no biologically significant or dose-related estrogen-like effects were observed at any doses below 7500 ppm in this study

There has been recent concern that BPA may exhibit weak antiandrogen activity, although Laudenbach *et al* (2001) reported no androgenic or antiandrogenic activity of BPA *in vivo* or *in vitro*, therefore, the current study data were compared to data from a recent study by McIntyre *et al* (2001) in which flutamide, an antiandrogen, was administered to rat dams by gavage on GD 12 21 at 0, 6 25, 12 5, 25, or 50 mg/kg/day F1 male offspring were examined for various androgen-mediated endpoints throughout life (Table 8). BPA did not affect any of the androgen-mediated endpoints affected by flutamide Therefore, BPA does not behave as a classic estrogen or as an antiandrogen, based on the data from other laboratories and from the present study

Conclusions

A strength of a multigeneration study, especially this one with 3 offspring generations, is that one can assess the reproducibility of a finding across offspring generations. the F0 parental generation is unique since it began exposure after puberty. The F1 and F2 offspring generations are comparable since they were exposed, at least potentially, *in utero* and during lactation through to adult reproduction and termination

TABLE 8
Comparison of Oral Flutamide and Dietary BPA on Selected Reproductive Endpoints

Effect	Flutamide dose	BPA	Comments
Reduced F1 offspring male AGD (PND 1)	≥ 6 25 mg/kg/day	No	BPA did not shorten male AGD at any dose
Areola nipple retention, F1 offspring males	≥ 6 25 mg/kg/day	No	BPA did not cause retention of areolae or nipples at any dose
Reproductive tract			
Cryptorchidism	≥ 6 25 mg/kg/day	No	BPA caused no cryptorchidism at any dose
Male malformations	≥ 6 25 mg/kg/day	No	BPA caused no male reproductive organ malformations at any dose
Reduced male organ weights			
Epididymides and accessory sex organs	≥ 6 25 mg/kg/day	No	BPA caused no reduction in both absolute and relative epididymal and accessory sex organ weights at any dose
Testes	≥ 6 25 mg/kg/day	No	BPA caused no reduction in both absolute and relative testes weights at any dose

Note Flutamide data taken from McIntyre *et al* (2001) (and therefore each serves as a replicate of the other). The F3 generation is comparable to the F1 and F2 generations, based on exposure *in utero* and during lactation through to adulthood, although the F3 animals were not mated prior to termination. The second strength of a multigeneration study is in the number of litters per group per generation, when the unit of statistical analysis is the litter, the larger the number of litters, the greater the statistical power. The third strength is use of continuous *ad libitum* exposure (via the diet) through multiple generations, encompassing prenatal, perinatal, postnatal, and peripubertal sensitive life stages.

In this study, BPA exhibited normal dose-response relationships across the entire dose range of 0.015 ppm (1 μg/kg/day) to 7500 ppm (500 mg/kg/day). BPA did not produce low-dose effects in an exposure scenario where animals were given *ad libitum* access to dietary concentrations of BPA, encompassing sensitive life stages (pre- and early postnatal development) and maturational portions of the life cycle, over 3 offspring generations. The results of this study do not support the hypothesis of low doses of BPA (at 1 μg/kg/day–5 mg/kg/day) causing adverse effects during any stage of the life cycle, including sensitive perinatal and peripubertal developmental periods, because there were only sporadic and obviously nontreatment-related effects observed across doses and generations.

The adult systemic toxicity no observed adverse effect level (NOAEL) was identified at 75 ppm (~ 5 mg/kg/day), and the reproductive and offspring toxicity NOAELs were 750 ppm (~ 50 mg/kg/day). Based on the absence of reproductive and developmental effects in offspring in this study, at doses where there was no significant maternal systemic toxicity, BPA should not be considered a selective reproductive or developmental toxicant.

ACKNOWLEDGMENTS

The authors wish to thank Ms L B Pelletier and Ms D A Wenzel, the RTI BPA Study Team, the rest of the RTI reproductive toxicology group, and the RTI Quality Assurance Unit Mr D L Brodish Manager. This study was sponsored by The Society of the Plastics Industry, Inc.

REFERENCES

Agresti, A (1990) *Categorical Data Analysis* John Wiley and Sons, New York

Armitage, P (1955) Test for linear trends in proportions and frequencies *Biometrics* **11**, 375–386

Ashby, J, and Tinwell, H (1998) Uterotrophic activity of bisphenol A in the immature rat *Environ Health Perspect* **106**(11), 719–720

Ashby, J, Tinwell, H, and Haseman, J (1999) Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed *in utero* *Regul Toxicol Pharmacol* **30**, 156–166

Atanassova, N, McKinnell, C, Turner, K J, Walker, M, Fisher, J S, Morley, M, Millar, M R, Groome, N P, and Sharpe, R M (2000) Comparative effects of neonatal exposure of male rats to potent and weak (environmental) estrogens on spermatogenesis at puberty and the relationship to adult testis size and fertility. Evidence for stimulatory effects of low estrogen levels *Endocrinology* **141**, 3898–3907

Biegel, L B, Cook, J C, Hurtt, M E, and O'Connor, J C (1998a) Effects of 17 β-estradiol on serum hormone concentrations and estrous cycle in female Crl CD BR rats. Effects on parental and first generation rats *Toxicol Sci* **44**, 143–154

Biegel, L B, Flaws, J A, Hirshfield, A N, O'Connor, J C, Elliott, G S, Ladics, G S, Silbergeld, E K, Van Pelt, C S, Hurtt, M E, Cook, J C, and Frame, S R (1998b) 90-day feeding and one-generation reproduction study in Crl CD BR rats with 17 β-estradiol *Toxicol Sci* **44**, 116–142

Cagen, S Z, Waechter, J M, Jr, Dimond, S S, Breslin, W J, Butala, J H, Jekat, F W, Joiner, R L, Shiotsuka, R N, Veenstra, G E, and Harris, L R (1999a) Normal reproductive development in CF-1 mice following prenatal exposure to bisphenol A *Toxicol Sci* **50**, 36–44

Cagen, S Z, Waechter, J M, Jr, Dimond, S S, Breslin, W J, Butala, J H, Jekat, F W, Joiner, R L, Shiotsuka, R N, Veenstra, G E, and Harris, L R (1999b) Normal reproductive organ development in Wistar rats exposed to bisphenol A in the drinking water *Regul Toxicol Pharmacol* **30**, 130–139

Carney, E W, Scortichini, B S, and Crissman, J W (1998) Feed restriction during *in utero* and neonatal life. Effects on reproductive and developmental end points in the CD rat *Toxicologist* **42**(Suppl 1), 102–103 (Abstract)

Cochran, W (1954) Some methods for strengthening the common χ^2 tests *Biometrics* **10**, 417–451

Cripps, A W, and Williams, V J (1975) The effect of pregnancy and lactation on food intake, gastrointestinal anatomy and the absorptive capacity of the small intestine in the albino rat *Br J Nutr* **33**, 17–32

Diel, P, Laudenbach, U, Smolnikar, K, Schulz, T, and Michna, H (2001a) Bisphenol A. Morphological and molecular uterine and mammary gland reactions in different strains of the rat (Wistar, Sprague-Dawley, Da/Han) *Toxicologist* **60**(1), 296 (Abstract)

Diel, P, Schmidt, S, Vollmer, G, and Michna, H (2001b) Comparison of the hormonal susceptibility of different rat strains to bisphenol A treatment *Reprod Toxicol* **15**(5), 590 (Proceedings Abstract)

Dodds, E C, and Lawson, W (1936) Synthetic oestrogenic agents without the phenanthrene nucleus *Nature* **137**, 996

Dunnett, C W (1955) A multiple comparison procedure for comparing several treatments with a control *J Am Stat Assoc* **50**, 1096–1121

Dunnett, C W (1964) New tables for multiple comparisons with a control *Biometrics* **20**, 482–491

Elswick, B A, Janszen, D B, Gould, J C, Stedman, D B, and Welsch, F (2000) Effects of perinatal exposure to low doses of bisphenol A in male offspring of Sprague-Dawley rats *Toxicologist* **54**(1), 256 (Abstract)

Ema, M, Fujii, S, Furukawa, M, Kiguchi, M, Ikka, T, and Harazono, A (2001) Rat two-generation reproductive toxicity study of bisphenol A *Reprod Toxicol* **15**, 505–523

Fialkowski, D and Chahoud, I (2000) The effects of low and high dose *in utero* exposure to bisphenol A on rat male offspring *Teratology* **61**(6), 484 (Abstract)

Gaido, K W, Leonard, L S, Lovell, S, Gould, J C, Babai, D, Portier, C J, and McDonnell, D P (1997) Evaluation of chemicals with endocrine modulating activity in a yeast-based steroid hormone receptor gene transcription assay *Toxicol Appl Pharmacol* **143**, 205–212

Gallavan, R H, Jr, Holson, J F, Stump, D G, Knapp, J F, and Reynolds, V L (1999) Interpreting the toxicologic significance of alterations in anogenital distance. Potential for confounding effects of progeny body weights *Reprod Toxicol* **13**, 383–390

Goloubkova, T, Ribeiro, M F, Rodrigues, L P, Cecconello, A L, and Spritzer, P M (2000) Effects of xenoestrogen bisphenol A on uterine and pituitary weight, serum prolactin levels and immunoreactive prolactin cells in ovariectomized Wistar rats *Arch Toxicol* **74**, 92–98

Gould, J C , Liaw J J , Elswick, B , Stedman, D , Turner, M , and Welsch, F (1998) Maternal effects and secretion into milk of low doses of Bisphenol A given to rats via drinking water *Toxicologist* **42**(Suppl 1), 175 (Abstract)

Gray, L E , Jr , and Ostby, J (1998) Effects of pesticides and toxic substances on behavioral and morphological reproductive development Endocrine versus nonendocrine mechanisms *Toxicol Ind Health* **14**, 159–184

Gray, L E , Jr , Ostby, J , Wolf, C , Lambright, C , and Kelce, W (1998) Annual review The value of mechanistic studies in laboratory animals for the production of reproductive effects in wildlife Endocrine effects on mammalian sexual differentiation *Environ Toxicol Chem* **17**(1), 109–118

Hanley T R , Jr , and Watanabe, P G (1985) Measurement of solid feed consumption patterns in neonatal rats by ^{141}Ce-radiolabeled microspheres *Toxicol Appl Pharmacol* **77**, 496–500

Jekat, F W , Twomey K , Butala, J H , Cagen, S Z , Dimond, S S , Joiner, R L Shiotsuka, R N , Stropp, G Veenstra, G E , and Waechter J M (2000) Evaluation of oestrogenic potential of bisphenol A in the uterotrophic assay by oral and parenteral route at extended dose ranges *Toxicologist* **54**(1) 261 (Abstract)

Jonckheere, A R (1954) A distribution-free k-sample test against ordered alternatives *Biometrika* **41**, 133–145

Kennedy, G C , and Mitra, J (1963) Body weight and food intake as initiating factors for puberty in the rat *Physiology* **166**, 408–418

Kim, H S , Han, S Y , Yoo, S D , Lee, B M , and Park, K L (2001) Potential estrogenic effects of bisphenol-A estimated by *in vitro* and *in vivo* combination assays *J Toxicol Sci* **26**, 111–118

Krishnan A V , Stathis, P , Permuth S F , Tokes, L , and Feldman, D (1993) Bisphenol A An estrogenic substance is released from polycarbonate flasks during autoclaving *Endocrinology* **132**, 2279–2286

Kubo K Arai, O Ogata, R , Omura, M , Hori, T , and Aou, S (2001) Exposure to bisphenol A during the fetal and suckling periods disrupts sexual differentiation of the locus coeruleus and of behavior in the rat *Neurosci Lett* **304**, 73–76

Kuiper, G G J , Carlsson, B , Grandien, K , Enmark, E , Haggblad, J , Nilsson, S , and Gustafsson, J A (1997) Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors α and β *Endocrinology* **138**, 863–870

Kuiper G G J , Lemmen, G , Carlsson, B , Corton, J C , Safe, S H , van der Saag, P T , van der Burg, B , and Gustafsson, J A (1998) Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta *Endocrinology* **139**, 4252–4263

Kwon S Stedman, D B , Elswick, B A , Cattley R C , and Welsch, F (2000) Pubertal development and reproductive functions of Crl CD BR Sprague-Dawley rats exposed to bisphenol A during prenatal and postnatal development *Toxicol Sci* **55**, 399–406

Laudenbach, U , Diel, P , Smolnikar, K , Schult, T , and Michna, H (2001) Bisphenol A does not mimic (anti-) androgen-like activities in orchiectomized Wistar rats *Toxicologist* **60**(1), 297 (Abstract)

Laws, S C , Carey, S A , Ferrell, J M , Bodman, G J , and Cooper, R L (2000) Estrogenic activity of octylphenol, nonylphenol, bisphenol A and methoxychlor in rats *Toxicol Sci* **54**, 154–167

Liaw, J J , Gould, J C Welsch, F , and Sar, M (1997) Gestation and early lactational influence of bisphenol A on the differentiation of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in rat brains *Toxicologist* **36**(1, Part 2) 14 (Abstract)

Liaw, J J , Stedman, D , Gould, J C Elswick, B , and Welsch F (1998) Reproductive development of female rats prenatally and lactationally exposed to bisphenol A *Toxicologist* **42**(Suppl 1), 176 (Abstract)

Long, X , Burke, K A , Bigsby, R M , and Nephew, K P (2001) Effects of the xenoestrogen bisphenol A on expression of vascular endothelial growth factor (VEGF) in the rat *Exp Biol Med (Maywood)* **226**, 477–483

Maruyama, S , Fujimoto, N , Yin H , and Ito, A (1999) Growth stimulation of a rat pituitary cell line MtT/E-2 by environmental estrogens *in vitro* and *in vivo* *Endocr J* **46**, 513–520

Matthews, J B , Twomey, K , and Zacharewski T R (2001) *In vitro* and *in vivo* interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors α and β *Chem Res Toxicol* **14**, 149–157

McIntyre, B S , Barlow, N J , and Foster, P M D (2001) Androgen-mediated development in male rat offspring exposed to flutamide *in utero* Permanence and correlation of early postnatal changes in anogenital distance and nipple retention with malformations in androgen-dependent tissues *Toxicol Sci* **62**, 236–249

Milligan, S R , Balasubramanian, A V , and Kalita, J C (1998) Relative potency of xenobiotic estrogens in an acute *in vivo* mammalian assay *Environ Health Perspect* **106**, 23–26

Morrissey, R E , George, J D , Price C J , Tyl, R W , Marr, M C , and Kimmel, C A (1987) The developmental toxicity of bisphenol A in rats and mice *Fundam Appl Toxicol* **8**, 571–582

Morrissey, R F , Lamb, J C , 4th, Morris, R W , Chapin, R F , Gulati, D K , and Heindel, J J (1989) Results and evaluations of 48 continuous breeding reproduction studies conducted in mice *Fundam Appl Toxicol* **13**, 747–777

Nagao, T , Saito, Y , Usumi, K , Kuwagata, M , and Imai, K (1999) Reproductive function in rats exposed neonatally to bisphenol A and estradiol benzoate *Reprod Toxicol* **13**, 303–311

Nagel, S C , vom Saal, F S , Thayer, K A , Dhar, M G , Boechler, M , and Welshons W V (1997) Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative *in vivo* bioactivity of the xenoestrogens bisphenol A and octylphenol *Environ Health Perspect* **105**, 70–76

NRC (1996) *Guide for the Care and Use of Laboratory Animals* Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council National Academy Press, National Institutes of Health

NTP (2001) National Toxicology Program Endocrine Disrupters Low-Dose Peer Review Available at http //ntp-server niehs nih gov/htdocs/liason/LowDosePeerFinalRpt pdf Accessed April 23, 2002

Pottenger L H , Domoradzki, J Y , Markham, D A , Hansen, S C , Cagen, S Z , and Waechter, J M Jr (2000) The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration *Toxicol Sci* **54**, 3–18

Quigley, C A De Bellis, A , Marschke, K B , el-Awady, M K , Wilson, E M , and French, F S (1995) Androgen receptor defects historical, clinical, and molecular perspectives *Endocr Rev* **16**, 271–321

Ramos, J , Varayoud, J , Sonnenschein, C , Soto, A M , Munoz de Toro, M , and Luque, E H (2001) Prenatal exposure to low doses of bisphenol A alters the periductal stroma and glandular cell function in the rat ventral prostate *Biol Reprod* **65**, 1271–1277

Robb, G W , Amann, R P , and Killian, G H (1978) Daily sperm production and epididymal sperm reserves of pubertal and adult rats *J Reprod Fertil* **54**, 103 107

Rubin, B S , Murray, M K , Damassa, D A , King, J C , and Soto, A M (2001) Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels *Environ Health Perspect* **109**, 675 680

SAS Institute (1989a) *SAS Language and Procedures Usage, Version 6*, 1st ed SAS Institute, Cary, NC

SAS Institute (1989b) *SAS/STAT Users' Guide, Version 6*, 4th ed , Volumes 1 and 2, SAS Institute, Cary, NC

SAS Institute (1990a) *SAS Language Reference, Version 6*, 1st ed , SAS Institute, Cary NC

SAS Institute (1990b) *SAS Language Procedures Guide, Version 6*, 3rd ed, SAS Institute, Cary NC

SAS Institute (1990c) *SAS Companion for the VMS™ Environment, Version 6*, 1st ed, SAS Institute, Cary, NC

SAS Institute (1996) *SAS Companion for the Microsoft Windows Environment* SAS Institute, Cary, NC

SAS Institute (1997) *SAS/STAT Software Changes and Enhancements Through Release 6 12* SAS Institute, Cary, NC

Schonfelder, G, Flick, B, Mayr L Talsness, C Paul, M, and Chahoud, I (2001) Molecular aspects of low and high dose Bisphenol A prenatal exposure *Reprod Toxicol* **15**, 594

Shah B V, Barnwell B G and Bieler, G S (1997) *SUDAAN® Software for the Statistical Analysis of Correlated Data User's Manual Release 7 5*, Volume 1 Research Triangle Institute, Research Triangle Park, NC

Sharpe R M, Fisher, J S, Millar, M M, Jobling, S, and Sumpter, J P (1995) Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production *Environ Health Perspect* **103**, 1136–1143

Sharpe R M, Turner, K J, and Sumpter, J P (1998) Endocrine disrupters and testis development *Environ Health Perspect* **106**, A220–A221

Shirley, B (1984) The food intake of rats during pregnancy and lactation *Lab Anim Sci* **34**, 169–172

Siegel, S (1956) *Nonparametric Statistics for the Behavioral Sciences* McGraw-Hill, New York

Snedecor G W, and Cochran, W G (1967) *Statistical Methods*, 6th ed, Iowa State University Press, Ames, IA

Snyder, R W, Maness, S C, Gaido, K W, Welsch, F, Sumner, S C J, and Fennell T R (2000) Metabolism and disposition of bisphenol A in female rats *Toxicol Appl Pharmacol* **168**, 225–234

Steinmetz R N Brown, N G, Allen, D L, Bigsby, R M, and Ben-Jonathan, N (1997) The environmental estrogen bisphenol A stimulates prolactin release *in vitro* and *in vivo* *Endocrinology* **138**, 1780–1786

Stoker, T E Robinette, C L, Britt, B H, Laws S C, and Cooper, R L (1999) Prepubertal exposure to compounds that increase prolactin secretion in the male rat Effects on the adult prostate *Biol Reprod* **61**, 1636–1643

Takahashi, O, and Oishi, S (2000) Disposition of orally administered 2,2-Bis (4-hydroxyphenylpropane (Bisphenol A) in pregnant rats and the placental transfer to fetuses *Environ Health Perspect* **108**, 931–935

Takahashi, O, and Oishi, S (2001) Testicular toxicity of dietary 2,2-bis(4-hydroxyphenyl) propane (bisphenol A) in F344 rats *Arch Toxicol* **75**, 42–51

Talsness, C E, and Chahoud, I (2000) The effects of *in utero* exposure to a low dose of bisphenol A on female sexual maturation of the rat *Teratology* **61**(6), 445 (Abstract)

Tohei, A, Suda, S, Taya, K, Hashimoto, T, and Kogo, H (2001) Bisphenol A inhibits testicular functions and increases luteinizing hormone secretion in adult male rats *Exp Biol Med (Maywood)* **226**, 216–221

U S EPA (1989) Toxic Substances Control Act, EPA (TSCA), Good Laboratory Practice Standards, Final Rule U S Environmental Protection Agency *Federal Register* **54**(158), 34034–34050

U S EPA (1996) Part II Environmental Protection Agency Reproductive Toxicity Risk Assessment Guidelines, Notice U S Environmental Protection Agency *Federal Register* **61**(212), 56274–56322 (31 October 1996)

U S EPA (1998) Health Effects Test Guidelines, OPPTS 870 3800, Reproduction and Fertility Effects (Final Guideline, August 1998) Office of Prevention Pesticides and Toxic Substances (OPPTS), Environmental Protection Agency

vom Saal, F S, Cooke, P S, Buchanan, D L, Palanza, P, Thayer, K A, Nagel, S C, Parmigiani, S, and Welshons, W V (1998) A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of the reproductive organs, daily sperm production, and behavior *Toxicol Ind Health* **14**, 239–260

Wazeter F X, and Goldenthal, E I (1984a) Report on reproduction and ninety day oral toxicity study in rats Report by the International Research and Development Corporation, Mattawan, MI (IRDC Report No 313-078) for the General Electric Company EPA/OTS, Doc No 40-8486013

Wazeter, F X, and Goldenthal, E I (1984b) Report on reproduction and ninety day feeding study in rats Report by the International Research and Development Corporation, Mattawan, MI (IRDC Report No 313-112) for the General Electric Company EPA/OTS, Doc No 40-8486013

Welsch, F, Elswick, B A, Janszen, D B, and Robinette, C L (2001) Lack of effects of perinatal exposure to low doses of bisphenol A on male rat offspring ventral prostate gland *Reproductive Toxicol* **15**(5), 597–598 (Proceedings Abstract)

Welsch, F, Elswick, B A, and Stedman, D B (2000) Effects of perinatal exposure to low doses of bisphenol A on female offspring of Sprague-Dawley rats *Toxicologist* **54**(1), 256 (Abstract No 1204)

Williams, K, McKinnell, C, Saunders, P T K, Walker, M, Fisher, J S, Turner K J Atanassova N, and Sharpe, M (2001) Neonatal exposure to potent and environmental oestrogens and abnormalities of the male reproductive system in the rat Evidence for importance of the androgen-oestrogen balance and assessment of the relevance to man *Hum Reprod Update* 7, 236–247

Winer, B J (1962) *Statistical Principles in Experimental Design* McGraw-Hill, New York

Wu, X and Chahoud, I (2000) The effects of low and high dose prenatal exposure on female rat offspring *Toxicologist* **54**(1), 255 (Abstract No 1200)

Yamasaki, K, Sawaki, M, and Takatsuki, M (2000) Immature rat uterotrophic assay of bisphenol A *Environ Health Perspect* **108**, 1147–1150