

**NCTR PROTOCOL E0219001**

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

**STATISTICAL REPORT**

**ANALYSIS OF VAGINAL CYTOLOGY DATA**

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## Statistical Analysis of Vaginal Cytology Data

### 1. Objectives

#### 1.1 Project Objectives

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

#### 1.2 Analysis Objectives

The goal of this analysis is to evaluate the effects of exposure to BPA in Sprague-Dawley rats on vaginal cytology data collected for 14 consecutive days at approximately 4 months of age.

### 2. Experimental Design

The study design consisted of first generation female and male rats (F<sub>0</sub>) for up to 600 mating pairs randomized to treatment groups in 5 litters. The goal of the F<sub>0</sub> matings was to obtain 352 study litters, 50 per dose group for vehicle controls and five BPA dose groups, 2.5, 25, 250, 2500, and 25000 µg/kg bw/day, and 26 for each of two EE<sub>2</sub> dose groups, 0.05 and 0.5 µg/kg bw/day. Dams were dosed daily from gestation day (GD) 6 until parturition. Dosing was by gavage for F<sub>0</sub> dams and F<sub>1</sub> pups, the second study generation. Litters were culled to 10 pups on PND 1. There were two study dosing arms of F<sub>1</sub> animals, daily continuous dosing to termination, and daily dose stopped at post-natal day (PND) 21. There was a vehicle control group and five BPA groups for each study dosing arm, and EE<sub>2</sub> daily dose groups for the continuous dosing arm only. From the F<sub>1</sub> litters, pups were allocated at weaning, PND 21, to the interim (1 year) and terminal (2 year) sacrifices for the core study. For vehicle and BPA terminal sacrifice groups, there were 50 pups each; for the interim sacrifice and the EE<sub>2</sub> terminal sacrifice groups, there were 20-26 pups each. Pups within litter and sex were assigned to different dosing arms and sacrifice times.

#### *Vaginal Cytology Data*

Vaginal opening and vaginal cytology data were collected from 13 cages randomly selected from each treatment group in the 2 year terminal sacrifice arm. The selected females were monitored from PND 22 until occurrence of vaginal opening. Beginning at 16 ± 2 weeks of age, vaginal smears were collected for 14 consecutive days.

### 3. Statistical Methods

Statistical analyses were performed separately for the BPA study arms, stop dose and continuous dose, and for the EE<sub>2</sub> continuous dose. Because pups within litter and sex were assigned to different dosing arms and sacrifice times, litter correlation is not a consideration for this study. Pairwise comparison tests were two-sided and all tests were conducted at the 0.05 significance level. Tests for trend, increased treatment effect with increasing dose, were performed for the BPA and vehicle control treatments.

Summary statistics are presented for proportions of days spent in estrus, diestrus, and proestrus for each animal and for estrous cycle length. For endpoint cycle length, cycle days were defined from the first day of estrus in one sequence of contiguous days to the first day of estrus in the following

sequence of stages. Cycles were considered censored if the last stage of data collection was either diestrus or proestrus.

Analyses were conducted on proportions of animals with abnormal cycles. The endpoints evaluated were any abnormal cycling, extended estrus, extended diestrus, and excessive proestrus. Extended estrus was defined by the principal investigator as more than 2 consecutive days of estrus; extended diestrus was defined as 4 or more consecutive days of diestrus; and excessive proestrus was defined as 2 or more consecutive days of proestrus in a cycle. For abnormal cycling defined by animal, the Cochran-Armitage method for binomial proportions was used to evaluate the pairwise differences in proportions. The two-sided p-value for the Fisher's exact test is reported for comparisons of dosed groups to control, and the one-sided Cochran-Armitage trend test was performed. Unadjusted and adjusted p-values using Holm's method are presented for pairwise comparisons of dosed groups to control.

For analysis of each endpoint, a sensitivity analysis was also performed. Of animals with vaginal cytology data, 94 core study animals (16 in vehicle control, 62 in BPA 2.5, 25, 250, 2500, and 25000  $\mu\text{g}/\text{kg}$  bw/day, and 16 in EE<sub>2</sub>  $\mu\text{g}/\text{kg}$  bw/day dose groups) were held during initial preweaning in the same rooms as a special BPA 250,000  $\mu\text{g}/\text{kg}$  bw/day high dose requested by an academic laboratory. In consultation with the Principal Investigator, to address the possibility of inadvertent exposure of the 94 core study animals, a sensitivity analysis excluding these animals was also performed to test the robustness of the results. Additional statistically significant pairwise comparisons from the sensitivity analysis are reported in the text.

## **4. Results**

Due to protocol deviations, there were eight animals in four cages with delayed monitoring of vaginal opening (UIN=23000529417, 23000529592, 23000531129, and 23000531379 in the EE<sub>2</sub> dose, UIN=23000529337 and 23000529402 in the vehicle continuous control, and UIN=23000529338 and 23000529403 in the vehicle stop dose control). The control dose animals were replaced by animals in the same load. However, because no replacements were available, data collected from the EE<sub>2</sub> dose animals are included in the analysis of vaginal cytology.

Results of core study analyses are presented in Appendix A for Tables and in Appendix B for Figures.

### **4.1 BPA Treatments Stop-Dose Arm**

Summary statistics for number of animals with vaginal cytology data in the BPA stop dose are presented in Table 1. Counts and percents of days in each estrus stage for each animal are summarized by dose in Table 2. Summary statistics for estrus cycle length are given in Table 3 (n is given for animals with at least one uncensored cycle).

Results of vaginal cycling abnormality analysis are presented in Table 4 for BPA stop dose. There were no statistically significant trends or pairwise comparisons of dose groups to control for BPA stop dose.

In the sensitivity analysis for BPA stop dose, there was a significant difference for total abnormal for BPA stop dose 25  $\mu\text{g}/\text{kg}$  bw/day compared to the vehicle control group ( $p=0.038$ ). The proportion of total abnormal in the BPA stop dose group was lower than in the vehicle control (5.0% abnormal in the dosed group compared to 33.3% abnormal in the control).

#### **4.2 BPA Treatments Continuous Dose Arm**

Summary statistics for number of animals with vaginal cytology data in the BPA continuous dose are presented in Table 5. Counts and percents of days in each estrus stage for each animal are summarized by dose in Table 6. Summary statistics for estrus cycle length are given in Table 7 (n is given for animals with at least one uncensored cycle).

Results of vaginal cycling abnormality analysis are presented in Table 8 for BPA continuous dose. There were no statistically significant trends or pairwise comparisons of dose groups to control for BPA continuous dose.

There were no additional statistically significant comparisons of the BPA continuous dose groups to vehicle control in the sensitivity analysis.

#### **4.3 EE<sub>2</sub> Treatments Continuous Dose**

Summary statistics for number of animals with vaginal cytology data in the EE<sub>2</sub> dose are presented in Table 9. Counts and percents of days in each estrus stage for each animal are summarized by dose in Table 10. Summary statistics for estrus cycle length are given in Table 11 (n is given for animals with at least one uncensored cycle).

Results of vaginal cycling abnormality analysis are presented in Table 12 for EE<sub>2</sub> dose. There were statistically significant differences in vaginal cycling abnormality for EE<sub>2</sub> 0.5 µg/kg bw/day compared to control for estrus abnormality (p<0.001, 96.2% compared to 11.5% abnormal) and total abnormality (p<0.001, 100.0% compared to 26.9% abnormal).

There were no additional statistically significant comparisons of the EE<sub>2</sub> dose groups to vehicle control in the sensitivity analysis.

### **5. Conclusions**

#### **5.1 BPA Treatments Stop-Dose Arm**

There were no statistically significant pairwise comparisons of dose groups to control for BPA stop dose.

In the sensitivity analysis for BPA stop dose, there was a significant difference for total abnormal for BPA 25 stop dose µg/kg bw/day compared to the vehicle control group. The proportion of total abnormal in the BPA stop dose group was lower than in the vehicle control.

#### **5.2 BPA Treatments Continuous Dose Arm**

There were no statistically significant pairwise comparisons of dose groups to control for BPA continuous dose.

#### **5.3 EE<sub>2</sub> Treatments Continuous Dose**

There were statistically significant differences in vaginal cycling abnormality for the EE<sub>2</sub> 0.5 µg/kg bw/day group compared to the vehicle control for estrus abnormality and total abnormality, with relatively higher abnormality in the dosed group compared to control.

## **Appendices**

### ***A. Statistical Tables***

*a. BPA Treatments Stop Dose Arm*

**Table 1. Summary of Animals with Vaginal Cytology Data for Bisphenol-A Stop-Dose**

<i>Dose</i>	<i>(<math>\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}</math>)</i>	<i>N</i>
Stop BPA	0	26
	2.5	26
	25	26
	250	26
	2500	26
	25000	26

**Table 2. Summary Statistics of Estrous Stage for Bisphenol-A Stop-Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )**

<i>Dose</i>	<i>Estrous Stage</i>	<i>Count</i>	<i>Percent</i>
0	Diestrus	203	56.4
	Proestrus	47	13.1
	Estrus	110	30.6
2.5	Diestrus	217	60.3
	Proestrus	33	9.2
	Estrus	110	30.6
25	Diestrus	189	52.4
	Proestrus	52	14.4
	Estrus	120	33.2
250	Diestrus	186	51.2
	Proestrus	55	15.2
	Estrus	122	33.6
2500	Diestrus	211	58.3
	Proestrus	50	13.8
	Estrus	101	27.9
25000	Diestrus	211	58.8
	Proestrus	37	10.3
	Estrus	111	30.9

**Table 3. Summary of Estrous Cycle Length (Days) for Bisphenol-A Stop-Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )<sup>1</sup>**

<i>0</i>			<i>2.5</i>			<i>25</i>			<i>250</i>			<i>2500</i>			<i>25000</i>		
<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>
20	4.08	0.12	22	4.23	0.13	23	4.17	0.12	25	4.47	0.23	26	4.42	0.15	24	4.38	0.17

<sup>1</sup> N includes animals with at least one uncensored cycle.



**Table 4. Comparison of Vaginal Cycling Abnormality by Animal Across Treatments**

<b>Bisphenol-A Stop-Dose (<math>\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}</math>)</b>																									
		<b>0</b>				<b>2.5</b>				<b>25</b>				<b>250</b>				<b>2500</b>				<b>25000</b>			
<b>Status</b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>		
Diestrus																									
Abnormal	5	19.2	0.200	5	19.2	1.000	1.000	2	7.7	0.418	1.000	1	3.8	0.190	0.953	4	15.4	1.000	1.000	5	19.2	1.000	1.000		
Normal	21	80.8	0.200	21	80.8	1.000	1.000	24	92.3	0.418	1.000	25	96.2	0.190	0.953	22	84.6	1.000	1.000	21	80.8	1.000	1.000		
Estrus																									
Abnormal	5	19.2	0.384	2	7.7	0.418	1.000	3	11.5	0.703	1.000	5	19.2	1.000	1.000	2	7.7	0.418	1.000	3	11.5	0.703	1.000		
Normal	21	80.8	0.384	24	92.3	0.418	1.000	23	88.5	0.703	1.000	21	80.8	1.000	1.000	24	92.3	0.418	1.000	23	88.5	0.703	1.000		
Proestrus																									
Abnormal	2	7.7	0.153	1	3.8	1.000	1.000	1	3.8	1.000	1.000	0	0.0	0.490	1.000	0	0.0	0.490	1.000	0	0.0	0.490	1.000		
Normal	24	92.3	0.153	25	96.2	1.000	1.000	25	96.2	1.000	1.000	26	100.0	0.490	1.000	26	100.0	0.490	1.000	26	100.0	0.490	1.000		
Total																									
Abnormal	10	38.5	0.330	7	26.9	0.555	1.000	5	19.2	0.220	1.000	6	23.1	0.367	1.000	6	23.1	0.367	1.000	8	30.8	0.771	1.000		
Normal	16	61.5	0.330	19	73.1	0.555	1.000	21	80.8	0.220	1.000	20	76.9	0.367	1.000	20	76.9	0.367	1.000	18	69.2	0.771	1.000		

<sup>1</sup> P-values are relative to the control group, except p-value for trend shown below control.

<sup>2</sup> P-values were adjusted for multiple comparisons using Holm's method.

**b. BPA Treatments Continuous Dose Arm**

**Table 5. Summary of Animals with Vaginal Cytology Data for Bisphenol-A Continuous**

<i>Dose</i>	<i>(<math>\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}</math>)</i>	<i>N</i>
BPA	0	26
	2.5	25
	25	26
	250	25
	2500	26
	25000	25

**Table 6. Summary Statistics of Estrous Stage for Bisphenol-A Continuous Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )**

<i>Dose</i>	<i>Estrous Stage</i>	<i>Count</i>	<i>Percent</i>
0	Diestrus	209	57.7
	Proestrus	50	13.8
	Estrus	103	28.5
2.5	Diestrus	188	54.0
	Proestrus	52	14.9
	Estrus	108	31.0
25	Diestrus	198	55.2
	Proestrus	40	11.1
	Estrus	121	33.7
250	Diestrus	172	49.4
	Proestrus	60	17.2
	Estrus	116	33.3
2500	Diestrus	217	59.9
	Proestrus	50	13.8
	Estrus	95	26.2
25000	Diestrus	194	55.7
	Proestrus	44	12.6
	Estrus	110	31.6

**Table 7. Summary of Estrous Cycle Length (Days) for Bisphenol-A Continuous Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )<sup>1</sup>**

<i>0</i>			<i>2.5</i>			<i>25</i>			<i>250</i>			<i>2500</i>			<i>25000</i>		
<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>
23	4.37	0.18	23	4.56	0.29	24	4.47	0.21	24	5.20	0.51	24	4.33	0.15	22	4.84	0.31

<sup>1</sup> N includes animals with at least one uncensored cycle.

**Table 8. Comparison of Vaginal Cycling Abnormality by Animal Across Treatments**

<b>Bisphenol-A Continuous Dose (<math>\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}</math>)</b>																									
		<b>0</b>				<b>2.5</b>				<b>25</b>				<b>250</b>				<b>2500</b>				<b>25000</b>			
<b>Status</b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>	<b>Count</b>	<b>Pct</b>	<b>P<sup>1</sup></b>	<b>P<sub>adj</sub><sup>2</sup></b>		
Diestrus																									
Abnormal	4	15.4	0.121	2	8.0	0.667	1.000	4	15.4	1.000	1.000	1	4.0	0.349	1.000	4	15.4	1.000	1.000	5	20.0	0.726	1.000		
Normal	22	84.6	0.121	23	92.0	0.667	1.000	22	84.6	1.000	1.000	24	96.0	0.349	1.000	22	84.6	1.000	1.000	20	80.0	0.726	1.000		
Estrus																									
Abnormal	3	11.5	0.345	3	12.0	1.000	1.000	4	15.4	1.000	1.000	4	16.0	0.703	1.000	2	7.7	1.000	1.000	4	16.0	0.703	1.000		
Normal	23	88.5	0.345	22	88.0	1.000	1.000	22	84.6	1.000	1.000	21	84.0	0.703	1.000	24	92.3	1.000	1.000	21	84.0	0.703	1.000		
Proestrus																									
Abnormal	0	0.0	0.182	0	0.0	-	-	0	0.0	-	-	1	4.0	0.490	1.000	1	3.8	1.000	1.000	1	4.0	0.490	1.000		
Normal	26	100.0	0.182	25	100.0	-	-	26	100.0	-	-	24	96.0	0.490	1.000	25	96.2	1.000	1.000	24	96.0	0.490	1.000		
Total																									
Abnormal	7	26.9	0.125	5	20.0	0.743	1.000	8	30.8	1.000	1.000	5	20.0	0.743	1.000	7	26.9	1.000	1.000	9	36.0	0.555	1.000		
Normal	19	73.1	0.125	20	80.0	0.743	1.000	18	69.2	1.000	1.000	20	80.0	0.743	1.000	19	73.1	1.000	1.000	16	64.0	0.555	1.000		

<sup>1</sup> P-values are relative to the control group, except p-value for trend shown below control.

<sup>2</sup> P-values were adjusted for multiple comparisons using Holm's method.

*c. EE<sub>2</sub> Treatments Continuous Dose*

**Table 9. Summary of Animals with Vaginal Cytology Data for Ethinyl Estradiol**

<i>Dose</i>	<i>(<math>\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}</math>)</i>	<i>N</i>
	0	26
EE2	0.05	26
	0.5	26

**Table 10. Summary Statistics of Estrous Stage for Ethinyl Estradiol ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )**

<i>Dose</i>	<i>Estrous Stage</i>	<i>Count</i>	<i>Percent</i>
0	Diestrus	209	57.7
	Proestrus	50	13.8
	Estrus	103	28.5
0.05	Diestrus	197	54.3
	Proestrus	40	11.0
	Estrus	126	34.7
0.5	Diestrus	56	15.5
	Proestrus	3	0.8
	Estrus	302	83.7

**Table 11. Summary of Estrous Cycle Length (Days) for Ethinyl Estradiol Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )<sup>1</sup>**

<i>0</i>		<i>0.05</i>			<i>0.5</i>			
<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>N</i>	<i>Mean</i>	<i>SE</i>
23	4.37	0.18	23	4.72	0.33	12	5.58	0.64

<sup>1</sup> N includes animals with at least one uncensored cycle.

**Table 12. Comparison of Vaginal Cycling Abnormality by Animal Across Treatments**

*Ethinyl Estradiol Dose ( $\mu\text{g}/\text{kg}_{\text{BW}}/\text{day}$ )*

<i>Status</i>	<i>0</i>		<i>0.05</i>		<i>0.5</i>		<i>P<sup>1</sup></i>	<i>P<sub>adj</sub><sup>2</sup></i>	<i>P<sup>1</sup></i>	<i>P<sub>adj</sub><sup>2</sup></i>
	<i>Count</i>	<i>Pct</i>	<i>Count</i>	<i>Pct</i>	<i>Count</i>	<i>Pct</i>				
Diestrus										
Abnormal	4	15.4	6	23.1	0.726	1.000	2	7.7	0.667	1.000
Normal	22	84.6	20	76.9	0.726	1.000	24	92.3	0.667	1.000
Estrus										
Abnormal	3	11.5	4	15.4	1.000	1.000	25	96.2	<.001	<.001
Normal	23	88.5	22	84.6	1.000	1.000	1	3.8	<.001	<.001
Total										
Abnormal	7	26.9	10	38.5	0.555	0.555	26	100.0	<.001	<.001
Normal	19	73.1	16	61.5	0.555	0.555	0	0.0	<.001	<.001

<sup>1</sup> P-values are relative to the control group.

<sup>2</sup> P-values were adjusted for multiple comparisons using Holm's method.

## ***B. Figures***

**Figure 1. Vaginal Cytology for BPA Stop Dose Vehicle Control**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	0	23000528234	D	D	P	E	D	D	P	E	D	D	D	D	D	D
Stop BPA	0	23000528306	D	D	D	P	E	E	E	E	E	E	E	E	E	E
Stop BPA	0	23000528349	E	E	D	D	D	P	E	D	D	D	P	E	D	D
Stop BPA	0	23000528433	D	D	D	D	D	P	P	E	D		E	D	D	D
Stop BPA	0	23000528720	P	E	E	E	E	E	E	E	E	E	E	E	E	E
Stop BPA	0	23000528941	D	D	D	P	E	D	D	P	E	D	D	E	E	D
Stop BPA	0	23000529161	E	D	D	P	E	D	D	D	E	D	D	P	E	D
Stop BPA	0	23000529296	P	E	D	D	D	E	D	D	P	E	D	D	D	E
Stop BPA	0	23000530300	D	E	D	D	D	E	D	D	D	E	D	D	P	E
Stop BPA	0	23000530388	E	D	D	D	E	D	D	P	E	D	D	P	E	D
Stop BPA	0	23000531465	P	E	D	D	E	E	E	D	D	P	E	E	D	D
Stop BPA	0	23000531653	D	E	D	D	D	D	E	E	D	P	E	E	D	D
Stop BPA	0	23000531667	D	D	P	E	D	D	P	E	D	D	E	E	D	D
Stop BPA	0	23000531680	D	E	D	D	D	D	D	D	D	D	D	D	D	D
Stop BPA	0	23000532532	D	D	D	D	D	D	D	E	D	D	D	E	D	D
Stop BPA	0	23000532662	D	E	D	D	E	E	D	D	P	E	D	D	D	D
Stop BPA	0	23000533022	E	D	D	D	D		D	D		E	D	D	P	
Stop BPA	0	23000533155	D	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	0	23000533242	P	E	D	D	D	P	E	D	P	E	E	E	E	E
Stop BPA	0	23000533290	D	D	D	D	P	E	D	D	D	D	D	D	D	D
Stop BPA	0	23000534214	D	D	E	D	D	P	E	D	D	E	E	D	D	D
Stop BPA	0	23000534438	P	P	D	D	D	P	E	E	P	E	E	E	D	D
Stop BPA	0	23000535475	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	0	23000535593	D	D	E	E	D	D	P	E	E	D	D	D	E	E
Stop BPA	0	23000535628	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	0	23000535641	D	P	E	D	D	P	E	D	D	P	E	D	D	P

**Figure 2. Vaginal Cytology for Stop Dose BPA 2.5 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	2.5	23000528289	D	D	P	E	D	D	P	E	D	D	E	E	D	D
Stop BPA	2.5	23000528321	D	E	E	D	D	D	D	P	E	D	D	E	E	D
Stop BPA	2.5	23000528477	D	D	P	E	E	E	E	E	E	E	E	E	E	E
Stop BPA	2.5	23000528520	P	E	D	D	D	P	E	D	D	E	E	D	D	P
Stop BPA	2.5	23000528698	P	E	D	D	D	P	E	D	D		E	D	D	E
Stop BPA	2.5	23000528956	D	D	P	E	D	D	D	E	D	D	D	D	D	D
Stop BPA	2.5	23000529256	D	P	E	D	D	D	D	D	D	D	D	D	D	D
Stop BPA	2.5	23000529449	P	E	D	D	D	E	D	D	P	E	D	D	D	E
Stop BPA	2.5	23000530312	D	P	E	E	D	D	D	E	E	D	D	D	E	E
Stop BPA	2.5	23000530411	D	E	D	D	D	E	E	D	D	D	E	E	D	D
Stop BPA	2.5	23000530600	D	D	E	E	E	D	D	D	D	E	D	D	D	E
Stop BPA	2.5	23000530761	D	E	E	D	D	P	E	E	D	D	D	E	D	D
Stop BPA	2.5	23000531473	E	E	D	D	D	E	E	D	D	D	E	E	D	D
Stop BPA	2.5	23000531520	D	D	D	D	D	D	D	D	D	P	P	D	E	D
Stop BPA	2.5	23000532607	D	D	D	P	E	D	D	D	E	E	D	D	P	E
Stop BPA	2.5	23000532749	D	D	P	E	D	D	P	E	D	D	E	E	D	D
Stop BPA	2.5	23000533169	D	D	D	E	D	D	D	E	D	D	P	E	D	D
Stop BPA	2.5	23000533371	D	D	D	P	E	D	D	E	D	D	D	D	D	D
Stop BPA	2.5	23000533564	D	E	E	D	D	E	E	D	D	E	E	D	D	E
Stop BPA	2.5	23000533707	E	E	D	D	E	E	D	D	P	E	D	D	P	E
Stop BPA	2.5	23000534062	D	D	D	E	D	D	D	D	D	D	D	D	D	D
Stop BPA	2.5	23000534390	D	D	P	E	D	D	P	E	D	D	D	E	D	D
Stop BPA	2.5	23000535117	D	D	D	D		P	E	E	D	D	E	E	D	D
Stop BPA	2.5	23000535131	E	D	D	P	E	D	D	E	E	D	D	E	E	D
Stop BPA	2.5	23000535481	D	D	P	E	E	D	D	P	E	D	D	P	E	D
Stop BPA	2.5	23000535508	D	D	E	D	D	P	E	D	D	D			E	D



**Figure 3. Vaginal Cytology for Stop Dose BPA 25 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	25	23000528259	D	E	D	D	D	E	E	D	D	P	E	D	D	D
Stop BPA	25	23000528273	P	E	D	D	D	P	E	E	D	D	D	E	E	D
Stop BPA	25	23000528399	E	D	D	D	E	E	D	D	D	P	E	E	E	D
Stop BPA	25	23000528593	D	D	E	D	D	D	D	D	D	P	P	D	D	D
Stop BPA	25	23000528966	E	E	E	E	E	E	E	E	E	E	D		E	E
Stop BPA	25	23000529094	E	E	E	D	D	E	E	E	E	E	E	D	E	E
Stop BPA	25	23000531082	D	E	D	D	P	E	D	D	P	E	D	D	E	E
Stop BPA	25	23000531144	D	P	E	D	D	P	E	D	D	E	E	D	D	P
Stop BPA	25	23000531237	D	E	D	D	P	E	D	D	D	E	D	D	E	E
Stop BPA	25	23000531318	D	P	E	D	D	D	D	E	E	D	D	E	D	D
Stop BPA	25	23000532545	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	25	23000532561	D	P	E	D	D	P	E	D	D	P		D	E	E
Stop BPA	25	23000532951	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	25	23000533181	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	25	23000533207	E	E	D	D	E	E	D	D	E	E	D	D	E	E
Stop BPA	25	23000533386	D	P	E	D	D	P	E	D	D	E	E	D	D	P
Stop BPA	25	23000533872	D	D	D	E	D	D		E	D	D	D	E	D	D
Stop BPA	25	23000533992	D	D	D	E	D	D	D	D	D	D	D	D	D	D
Stop BPA	25	23000534416	D	P	E	D	D	D	E	E	D	E	E	D	D	P
Stop BPA	25	23000534779	D	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	25	23000534797	P	E	D	D	D	P	E	D	D	D	D	E	E	D
Stop BPA	25	23000534942	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	25	23000535710	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	25	23000535958	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	25	23000536073	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	25	23000536088	D	P	E	D	D	P	E	D	D	P	E	D	D	P

**Figure 4. Vaginal Cytology for Stop Dose BPA 250 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	250	23000528184	E	D	D	D	D	E	D	D	D	E	D	D	D	P
Stop BPA	250	23000528248	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Stop BPA	250	23000528446	E	E	D	D	D	P	E	D	D	E	E	E	D	D
Stop BPA	250	23000528630	E	E	E	E	D	D	D	P	E	D	D	D	E	E
Stop BPA	250	23000528680	E	E	E	E	E	E	D	D	P	E	E	E	D	D
Stop BPA	250	23000528788	E	E	D	D	D	P	E	E	E	E	D	D	D	D
Stop BPA	250	23000530681	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	250	23000530723	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	250	23000530816	D	E	D	D	P	E	D	D	P	E	D	D	E	E
Stop BPA	250	23000531022	E	D	D	P	E	D	D	D	E	D	D	P	E	D
Stop BPA	250	23000531034	E	E	E	D	D	P	E	D	D	P	E	D	D	P
Stop BPA	250	23000531305	D	D	P	E	D	D	D	E	D	D	P	E	D	D
Stop BPA	250	23000532885	D	D	E	D	D	D	E	D	D	D	E	D	D	D
Stop BPA	250	23000533042	E	D	D	D	E	D	D	D	E	D	D	D	D	D
Stop BPA	250	23000533075	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	250	23000533257	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	250	23000533396	E	D	D	E	E	D	D	P	E	D	D	P	E	D
Stop BPA	250	23000533628	D	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	250	23000534169	D	P	E	E	D	D	D	P	E	D	D	P	E	D
Stop BPA	250	23000534284	D	D	P	E	D	D		E	D	D	P	E	D	D
Stop BPA	250	23000534304	E	D	D	P	E	D	D	D	E	D	D	E	E	D
Stop BPA	250	23000534430	D	P	E	D	D	E	E	D	D	P	E	D	D	P
Stop BPA	250	23000535679	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	250	23000535946	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	250	23000535976	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	250	23000536054	E	D	D	P	E	D	D	P	E	D	D	P	E	D

**Figure 5. Vaginal Cytology for Stop Dose BPA 2500 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	2500	23000528223	D	D	E	E	D	D	D	P	E	D	D	D	D	E
Stop BPA	2500	23000528336	E	E	D	D	D	D	E	D	D	D	D	E	D	D
Stop BPA	2500	23000528361	P	E	D	D	D	E	D	D	D	E	D	D	D	E
Stop BPA	2500	23000528875	E	D	D	D	E	E	D	D	D	D	D	E	D	D
Stop BPA	2500	23000529083	D	D	E	E	D	D	D	P	E	D	D	D	D	D
Stop BPA	2500	23000529188	D	D	E	E	D	D	D	P	E	D	D	D	E	D
Stop BPA	2500	23000530376	E	D	D	P	E	D	D	D	E	D	D	P	E	D
Stop BPA	2500	23000530439	D	E	D	D	P	E	D	D	P	E	D	D	D	E
Stop BPA	2500	23000530507	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	2500	23000530534	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	2500	23000530559	E	D	D	P	E	D	D	D	D	D	D	D	D	D
Stop BPA	2500	23000530793	D	P	E	D	D	P	E	D	D	P	E	D	D	P
Stop BPA	2500	23000531404	D	P	E	D	D	P	E	D	D	P	E	D	D	P
Stop BPA	2500	23000531429	D	P	E	D	D	D	D	E	D	D	E	E	E	D
Stop BPA	2500	23000532492	D	E	E	D	D	E	E	D	D	P	E	D	D	E
Stop BPA	2500	23000532713	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	2500	23000532828	P	E	D	D	P	E	D	D	E	E	D	D	P	E
Stop BPA	2500	23000533106	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	2500	23000533299	D	D	P	E	D	D	P	E	D	D	P	E	D	D
Stop BPA	2500	23000533328	D	D	P	E	D	D	E	E	D	D	P	E	D	D
Stop BPA	2500	23000533340	E	E	D	D	D	D	D	D	E	E	D	D	P	E
Stop BPA	2500	23000533510	D	D	D	E	E	E	D	D	E	D	D	E	E	D
Stop BPA	2500	23000534352	E	D	D	E	E	D	D	P	E	D	D	P	E	
Stop BPA	2500	23000534717	D	D	P	D	D	D	D	E	D	D	D	D	E	D
Stop BPA	2500	23000536248	E	D	D	P	E	D	D	P	E	D	D	P	E	D
Stop BPA	2500	23000536314	D	D	P	E	D	D	P	E	D	D	P	E	D	

**Figure 6. Vaginal Cytology for Stop Dose BPA 25000 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
Stop BPA	25000	23000528194	D	D	D	D	D	D	D	E	D	D	D	D	D	D
Stop BPA	25000	23000528419	E	E	E	P	E	E	D	D	E	E	E	E	E	E
Stop BPA	25000	23000528459	D	D	E	D	D	D	D	P	E	D	D	D	P	E
Stop BPA	25000	23000528492	E	E	E	D	E	E	E	D	E	E	D	D	D	D
Stop BPA	25000	23000528738	D	D	P	E	D	D	D	P	E	D	D	D	D	D
Stop BPA	25000	23000528748	E	E	E	E	E	E	D	D	E	D	D	D	E	D
Stop BPA	25000	23000530322	D	P	E	D	D	P	E	D	D	P	E	D	D	E
Stop BPA	25000	23000530470	P	E	D	D	P	E	D	D	P	E	D	D	P	E
Stop BPA	25000	23000530544	D	D	D	D	D	P	D	D	D	E	D	D	D	D
Stop BPA	25000	23000530663	P	E	D	D	D	E	D	D	P	E	D	D	E	E
Stop BPA	25000	23000530701	D	E	D	D	D	E	D	D	D	E	D	D	D	E
Stop BPA	25000	23000530714	D	D	P	E	D	D	P	E	D	D	E	E	D	D
Stop BPA	25000	23000531605	D	E	D	D	D	D	P	E	E	D	D	E	D	D
Stop BPA	25000	23000531622	D	D	D	D	D	E	D	D	D	E	D	D	D	D
Stop BPA	25000	23000532623	D	E	D	D	E	P	E	D	E	E	D	D	D	E
Stop BPA	25000	23000532634	D	D	E	E	D	D	D	P	E	D	D		E	E
Stop BPA	25000	23000532844	E	D	D	E	E	D	D	P	E	D	D		E	D
Stop BPA	25000	23000532965	D	D	E	E	D	D	D	P	E	E	D	D	D	E
Stop BPA	25000	23000533220	D	D	E	D	D	P	E	D	D	P	E	D	D	P
Stop BPA	25000	23000533447	D	E	D	D	D	D	P	E	D	D	P	E	D	D
Stop BPA	25000	23000533466	D	D	E		D	D	E	D	D	P	E	D	D	P
Stop BPA	25000	23000533593	E	E	D	D	P	E	D		P	E	D		P	E
Stop BPA	25000	23000534866	E	D	D	D	E	E	D	D	D	D	D	D	D	D
Stop BPA	25000	23000534897	D	E	D	D	D	P	E	D	D	D	E	E	D	D
Stop BPA	25000	23000535722	E	E	D	D	D	E	E	D	D	D	P	E	D	D
Stop BPA	25000	23000535769	D	D	P	E	D	D	P	E	D	D	P	E	D	D

**Figure 7. Vaginal Cytology for Continuous Dose Vehicle Control**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	0	23000528233	D	D	P	E	D	D	D	P	E	D	D	D	E	D
BPA	0	23000528305	P	E	E	E	E	E	E	E	E	E	D	D	D	D
BPA	0	23000528348	D	E	E	D	D	D	P	E	D	D	P	E	D	D
BPA	0	23000528432	E	E	D	E	E	E	E	E	E	D	D	D	P	E
BPA	0	23000528719	E	E	D	D	D	D	P	E	D	D	D	D	D	D
BPA	0	23000528940	P	E	D	D	D	E	D	D	D	P	E	D	D	D
BPA	0	23000529160	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	0	23000529295	P	E	D	D	D	D	D	D	D	D	D	D	D	D
BPA	0	23000530299	D	E	D	D	D	E	D	D	E	E	D	D	P	E
BPA	0	23000530390	D	D	D	E	E	D	D	D	E	E	D	D	P	E
BPA	0	23000531462	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	0	23000531652	D	D	P	E	D	D	P	E	D	D	E	E	D	D
BPA	0	23000531666	D	D		E	D	D	E	E	E	D	E	E	E	D
BPA	0	23000531679	D	D	D	D		D	D	D	D	D	D	D	D	D
BPA	0	23000532531	D	D	P	E	D	D	D	E	D	D	D	P	E	D
BPA	0	23000532661	P	D	D	D	D	E	D	D	P	E	D	D	D	D
BPA	0	23000533021	D	P	E	D	D	P	E	D	D	P	E	D	D	D
BPA	0	23000533154	D	D	D	D	D	D	E	D	D	P	E	D	D	P
BPA	0	23000533241	D	D	P	E	D	D	P	E	E	D	D	D	E	E
BPA	0	23000533289	D	D	P	E	D	D	D	E	D	D	P	E	D	D
BPA	0	23000534213	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	0	23000534634	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	0	23000534744	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	0	23000534759	D	E	E	D	D	P	E	D	D	E	E	D	D	P
BPA	0	23000535592	D	D	E	E	D	D	P	E	D	D	E	E	D	D
BPA	0	23000535640	E	D	D	P	E	D	D	P	E	D	D	P	E	D

**Figure 8. Vaginal Cytology for Continuous Dose BPA 2.5 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	2.5	23000528288	D	D	D	P	D	D	D	P	E	E	D	D	D	P
BPA	2.5	23000528320	E	E	E	E	D	D	D	D	E	E	D	D	D	E
BPA	2.5	23000528476	D	D	D	P	E	E	E	E	E	D	D	D	E	E
BPA	2.5	23000528697	E	E	E	E	E	D	D	D	D	E	D	D	D	P
BPA	2.5	23000528955	E	E	D	D	D	E	D	D	D	D	D	D	D	P
BPA	2.5	23000529255	P	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	2.5	23000529443	E	D	D	E	E	D	D	P	E	D	D	P	E	D
BPA	2.5	23000530311	P	E	D	D	E	E	D	D	P	E	D	D	E	E
BPA	2.5	23000530414	D	E	E	D	D	D	E	E	D	D	D	E	E	D
BPA	2.5	23000530599	E	D	D	P	E	D	D	D	E	D	D	P	E	D
BPA	2.5	23000530760	E	D	D	P	E	D	D	E	E	D	D	E	E	D
BPA	2.5	23000531472	D	P	E	D	D	P	E	D	D	E	E	D	D	D
BPA	2.5	23000531519	D	E	D	D	D	E	D	D	P	E	D	D	P	E
BPA	2.5	23000532606	D	D	D	D	P	E	D	D	P	E	E	D	D	E
BPA	2.5	23000532748	E	D	P	E	D	D	D	P	E	D	D	D	D	E
BPA	2.5	23000533168	D		E	E	D	P	E	D	D	P	E	D	D	E
BPA	2.5	23000533370	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2.5	23000533561	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2.5	23000533706	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2.5	23000534063	D	P	E	D	D	D	D	D	D	D	D	D	D	D
BPA	2.5	23000534391	D	P	E	D	D		P	E	D	D	D	P	E	D
BPA	2.5	23000535480	D	D	P	E	D	D	P	E	D	D	P	E	D	D
BPA	2.5	23000535497	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2.5	23000535507	E	D	D	P	E	D	D	P	E	D	D	D	E	D
BPA	2.5	23000535661	P	E	D	D	P	E	D	D	P	E	D	D	P	E

**Figure 9. Vaginal Cytology for Continuous Dose BPA 25 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	25	23000528258	E	E	D	D	D	D	E	E	D	D	D	E	D	D
BPA	25	23000528272	D	D	D	E	D	D	D	E	D	D	D	E	D	D
BPA	25	23000528398	E	E	E	E	E	E	D	D	D	E	E	D	D	E
BPA	25	23000528592	E	D	D	D	D	E	D	D	D	E	D	D	D	E
BPA	25	23000528965	E	E	E	E	E	E	D	E	D	E	E	E	D	E
BPA	25	23000529093	E	E	E	E	E	E	E	D	E	E	E	E	E	E
BPA	25	23000531081	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	25	23000531143	P	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	25	23000531234	P	E	D	D	D	E	E	D	D	E	D	D	D	D
BPA	25	23000531320	D	D	D	E	E	D	D	D	E	E	D	D	D	E
BPA	25	23000532544	D		E	D	D	P	E	D	D	D	E	D	D	P
BPA	25	23000532560	P	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	25	23000532950	D	D	E	D	D	D	P	E	D	D	D		E	E
BPA	25	23000533180	P	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	25	23000533206	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	25	23000533384	D	D	P	E	D	D	P	E	D	D	P	E	D	D
BPA	25	23000533871	E	D	D	E	E	D	D	P	E	D	D		E	
BPA	25	23000533991	D	D	E	D	D	P	E	D	D	D	E	D	D	D
BPA	25	23000534778	P	E	D		P	E	E	D	E	E	D	E	E	E
BPA	25	23000534824	D	D	D	D	D	P	D	D	D	E	E	D	D	D
BPA	25	23000534851	E	D	D	P	E	D	D	P	E	E	D	P	E	D
BPA	25	23000534941	D	D	P	E	D	D	P	E	D	D	E	E	D	D
BPA	25	23000535957	D	D	D	D	D	E	D	D	E	E	D	D	D	E
BPA	25	23000536072	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	25	23000536111	D	D	D	D	D	D	D	D	D	D	D	E	D	D
BPA	25	23000536207	D	D	E	E	D	D	D	E	D	D	D	D	D	E

**Figure 10. Vaginal Cytology for Continuous Dose BPA 250 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	250	23000528246	P	E	E	E	E	E	E	E	E	E	D	E	E	E
BPA	250	23000528445	E	E	D	D	D	D	E	E	D	D	D	E	E	D
BPA	250	23000528629	P	E	D	D	D	D	P	E	E	D	D	D	P	E
BPA	250	23000528679	D	P	E	D	D	D	P	E	D	D	D	D	E	D
BPA	250	23000528787	E	E	E	E	E	E	E	E	E	E	E	E	E	E
BPA	250	23000530680	E	D	D	P	E	D	D	P	E	D	D	E	E	D
BPA	250	23000530722	E	D	D	P	P	P	P	P	P	P	P	E	E	E
BPA	250	23000530815	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	250	23000531020	P	E	D	D	D	P	E	D	D	P	E	D	D	E
BPA	250	23000531033	P	E	D	D	D	D	E	D	D	P	E	D	D	E
BPA	250	23000531304	D	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	250	23000532884	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	250	23000533044	D	D	P	E	D	D	D	P	E	D	D	P	E	E
BPA	250	23000533074	D	P	E	D	D	D	P	E	D	D	D	P	E	D
BPA	250	23000533256	E	D	D	E	E	E	E	E	D	D	D	D	E	D
BPA	250	23000533395	D	P	E	D	D	P	E	D	D	P	E	D	D	E
BPA	250	23000533627	D	D	D	E	D	D	D	E	D	D	D	E	D	D
BPA	250	23000534168	D	E	D	D	P	E	D	D	P	E	D	D	P	E
BPA	250	23000534283	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	250	23000534303	D	P	E	D	D	P	E	D	D	E	E	D	D	P
BPA	250	23000534429	D	P	E	D	D		E	D	D	D	E	D	D	
BPA	250	23000535678	E	D	D	D	D	D	D	D	D	D	D	D	P	E
BPA	250	23000535945	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	250	23000535975	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	250	23000536053	D	D	E	D	D	P	E	D	D	P	E	D	D	D



**Figure 11. Vaginal Cytology for Continuous Dose BPA 2500 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	2500	23000528222	E	D	D	D	P	E	D	D	D	E	E	E	E	E
BPA	2500	23000528335	E	E	E	D	D	E	E	E	D	D	D	D	E	D
BPA	2500	23000528360	D	D	D	D	D	D	D	D	D	P	D	D	D	P
BPA	2500	23000528872	D	D	D	D	D	D	D	D	D	D	D	E	D	D
BPA	2500	23000529082	D	D	D	D	D	E	D	D	D	P	E	D	D	D
BPA	2500	23000529187	E	D	D	D	E	D	D	D	D	E	E	D	D	D
BPA	2500	23000530375	E	D	D	P	E	D	D	D	D	E	D	D	E	D
BPA	2500	23000530438	E	D	D	P	E	D	D	D	D	E	D	D	E	D
BPA	2500	23000530506	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	2500	23000530533	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2500	23000530558	E	D	D	P	E	D	D	P	E	D	D	D	E	D
BPA	2500	23000530792	E	D	D	P	E	D	D	P	E	D	D	P	E	D
BPA	2500	23000531403	D	D	D	E	D	D	P	E	D	D	E	E	D	D
BPA	2500	23000531428	D	P	E	D	D	E	E	D	D	P	E	D	D	P
BPA	2500	23000532491	E	E	D	D	E	E	D	D	P	E	D	D	E	E
BPA	2500	23000532712	D	D	P	E	D	D	P	P	P	P	E	D	D	E
BPA	2500	23000532827	D	D	P	E	D		P	E	D	D	P	E	D	D
BPA	2500	23000533104	E	D	D	P	E	D	D	D	P	D	D	D	D	E
BPA	2500	23000533298	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	2500	23000533326	D	D	E	D	D	P	E	D	D	P	E	D	D	P
BPA	2500	23000533339	D	D	E	D	D	D	P	E	D	D	P	E	D	D
BPA	2500	23000533509	D	D	D	E	E	D	D	D	E	D	D	D	D	E
BPA	2500	23000534607	E	D	D	D	D	E	D	D	D	D	D	D	D	D
BPA	2500	23000534716	D	P	E	D	D	D	E	D	D	P	E	D	D	P
BPA	2500	23000535419	D	D	E	E	D	D	P	E		D	E	E	D	D
BPA	2500	23000535540	P	E	D	D	P	E	D	D	D	E	D	D	P	E

**Figure 12. Vaginal Cytology for Continuous Dose BPA 25000 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
BPA	25000	23000528193	E	E	E	D	D	D	D	E	D	D	D	D	E	E
BPA	25000	23000528418	E	E	E	E	E	E	E	E	E	E	E	E	E	E
BPA	25000	23000528457	E	E	E	E	E	E	E	E	E	E	E	D	D	P
BPA	25000	23000528491	E	E	E	E	E	E	D	D	D		P	E	E	E
BPA	25000	23000528737	D	D	D	D	D	P	E	D	D	E	E	D	D	D
BPA	25000	23000528747	D	D	D	D	E	E	D	D	D	D	E	E	D	D
BPA	25000	23000530321	D	D	D	D	D	E	D	D	D	E	E	D	D	E
BPA	25000	23000530469	P	E	D	D	P	E	D	D	E	E	D	D	P	E
BPA	25000	23000530543	E	D	D	P	E	D	D	D	D	D	D	D	D	D
BPA	25000	23000530700	P	E	D	D	P	E	D	D	P	E	D	D	D	E
BPA	25000	23000530713	P	P	D	D	D	D	D		P	P	P	P	D	P
BPA	25000	23000531604	E	D	D	D	E	D	D	D	E	D	D	D	E	D
BPA	25000	23000532621	D	E	E	D	D	P	E	D	D	P	E	D	D	P
BPA	25000	23000532633	D	D	D	E	E	D	D	D	P	E	D	D	D	P
BPA	25000	23000532843	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	25000	23000532964	E	D	D	D	E	D	D	D	E	D	D	D	E	D
BPA	25000	23000533118	D	D	P	E	D	D	P	E	D	D	P	E	D	D
BPA	25000	23000533128	E	D	D	P	E	D	D	D	P	E	D	D	D	D
BPA	25000	23000534259	D	E	D	D	D	D	P	E	D	D	D	E	D	D
BPA	25000	23000534376	D	E	D	D	P	E	D	D	E	E	D	D	P	E
BPA	25000	23000534401	D	D	D	E	E	D	D	D	D	E	E	D	D	P
BPA	25000	23000535721	D	P	E	D	D	P	E	D	D	P	E	D	D	P
BPA	25000	23000536137	E	D	D	D	D	P	E	D	D	D	D	D	D	D
BPA	25000	23000536474	E	D	D	D	D	P	E	D	D	D	D	E	D	D
BPA	25000	23000536549	E	D	D	P	E	D	D	P	E	D	D	P	E	D

**Figure 13. Vaginal Cytology for Continuous EE<sub>2</sub> Dose 0.05 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
EE2	0.05	23000528534	E	E	D	D	D	E	D	D	D	D	D	D	D	D
EE2	0.05	23000528577	P	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.05	23000529020	E	D	D	D	D	D	P	E	D	D	D	D	D	D
EE2	0.05	23000529270	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.05	23000529286	E	E	E	E	E	E	E	E	E	D	E	E	E	E
EE2	0.05	23000529327	E	E	D	D	D	D	D	D	E	D	D	D	D	D
EE2	0.05	23000530630	D	D	D	E	D	D	D	E	D	D	D	E	D	D
EE2	0.05	23000530754	D	D	D	D	D	D	D	D	D	D	D	D	D	D
EE2	0.05	23000531099	D	D	P	E	D	D	D	E	D	D	P	E	D	D
EE2	0.05	23000531210	D	D	P	E	D	D	P	E	D	D	P	E	D	D
EE2	0.05	23000531224	P	E	D	D	P	E	D	D	E	E	D	D	P	E
EE2	0.05	23000531416	P	E	D	D	D	E	E	D	D	P	E	D	D	E
EE2	0.05	23000532805	D	D	P	E	D	D	P	E	E	D	E	E	D	D
EE2	0.05	23000532995	D	P	E	D	D	D	E	D	D	D	D	D	D	D
EE2	0.05	23000533455	D	E	E	E	D	D	D	E	E	D	D	D	E	E
EE2	0.05	23000533523	D	E	E	D	D	D	E	E	D	D	D	D	E	E
EE2	0.05	23000533857	D	P	E	D	D	P	E	D	D	E	E	D	D	E
EE2	0.05	23000533944	E		D	D	D	E	D	D	D	D	E	D	D	D
EE2	0.05	23000534188	E	D	D	P	E	D	D	P	E	D	D	P	E	D
EE2	0.05	23000534485	E	D	D	P	E	D	D	P	E	D	D	P	E	D
EE2	0.05	23000534648	P	E	D	D	P	E	D	D	P	E	D	D	P	E
EE2	0.05	23000534661	D	D	P	E	D	D	P	E	D	D	P	E	D	D
EE2	0.05	23000534732	P	E	D	D	P	E	D	D	E	E	D	D	P	E
EE2	0.05	23000534930	E	D	D	P	E	D	D	P	E	D	D	P	E	D
EE2	0.05	23000535580	E	D	D	P	E	D	D	D	E	D	D	D	D	D
EE2	0.05	23000535737	P	E	D	D	D	D	P	E	D	D	P	E	D	E

**Figure 14. Vaginal Cytology for Continuous EE<sub>2</sub> Dose 0.5 µg/kg bw/day**

Compound	Dose	UIN	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12	Day13	Day14
EE2	0.5	23000528168	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000528375	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000528383	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000528910	E	E	E	D	E	E	E	E	D	D	E	D	D	D
EE2	0.5	23000528925	E	E	E	D	E	E	E	E	E	D	E	E	D	E
EE2	0.5	23000529007	E	E	E	E	E	E	E		E	E	E	D	D	E
EE2	0.5	23000529050	D	E	E	E	D	E	E	D	D	E	E	D	E	D
EE2	0.5	23000529389	E	E	E	E	E	E	D	E	E	D	D	E	E	E
EE2	0.5	23000529417	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000529592	E	E	D	E	E	E	E	E	E	D	D	D	E	E
EE2	0.5	23000530333	D	D	D	D	D	D	E	E	E	E	E	E	E	E
EE2	0.5	23000530353	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000530453	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000530670	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000530738	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000530844	D	E	E	E	D	E	E	E	E	E	E	D	E	E
EE2	0.5	23000531129	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000531379	E	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000532698	E	E	E	D	E	E	E	D	E	E	D	E	E	E
EE2	0.5	23000532761	E	E	D	D	P	E	D	D	P	E	E	E	D	E
EE2	0.5	23000533007	E	E	E	E	E	E	E		E	E	E	E	D	E
EE2	0.5	23000533419	E	E	E	E	E	E	E	E	E	E	D	D	E	E
EE2	0.5	23000533958	D	E	E	E	E	E	E	E	E	E	E	E	E	E
EE2	0.5	23000534814	D	E	E	E	E	E	E	E	E	E	E	E	E	
EE2	0.5	23000535395	D	D	D	E	D	D	D	D	P	E	E	E	D	D
EE2	0.5	23000535456	E	E	E	E	E	E	E	E	E	E	E	E	E	E

### ***C. Data***

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

## Quality Control

### 1. *Data Verification*

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

### 2. *Computer Program Verification*

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

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

### 3. *Statistical Report Review*

#### 3.1 *Statistical Report Text*

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

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

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

#### 3.2 *Table Verification*

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

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

#### 3.3 *Graph Verification*

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

### 4. *Conclusions*

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