Statistical Report

Project #:	E2190.03
Project Title:	Two Year Chronic Toxicology Study of Bisphenol A (BPA) [CAS # 80-05-7] Administered by Gavage to Sprague-Dawley Rats (NCTR) from Gestational Day 6 Until Birth and Directly to F1 Pups from Postnatal Day 1 (PND 1); Continuous and Stop Dose (PND 21) Exposures
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Task:	Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice) - Addendum
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Statistical Analysis of Neoplastic and Non-neoplastic Lesions (Interim Sacrifice) - Addendum

1. Objectives

1.1 Project Objectives

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

1.2 Analysis Objectives

The objective of this analysis is to determine the effects on histopathology of a broad range of continuous and stop doses of BPA after two years. Statistical analyses of data from continuous doses of the reference estrogen EE_2 are also presented. This addendum presents analyses regarding pooled adenomas and carcinomas for the pituitary gland, as this pool was not included in the original statistical report.

2. Experimental Design

The study design consisted of first generation female and male rats (F_0) for up to 600 mating pairs randomized to treatment groups in 5 loads. The goal of the F_0 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_2 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_0 dams and F_1 pups, the second study generation. Litters were culled to 10 pups on PND 1.There were two study dosing arms of F_1 animals, daily continuous dosing to termination, and daily dose stopped at post-natal day (PND) 21. There was a vehicle control group and five BPA groups (2.5, 25, 250, 2500, and 25000 µg/kg) for each study dosing arm, and EE_2 daily dose groups (0.05 and 0.50 µg/kg) for the continuous dosing arm only. From the F_1 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_2 terminal sacrifice groups, there were 20-26 pups each. Pups within litter and sex were assigned to different dosing arms and sacrifice times.

3. Statistical Methods

Statistical analyses were performed separately for the BPA study arms, stop dose and continuous dose, and for the EE_2 continuous dose.

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

Pituitary gland adenoma and carcinoma pooled lesions with an incidence of two or more in any treatment group were included in each analysis. The tests for the comparisons to vehicle are one-sided, while the trend tests are two-sided. No adjustments are made for multiplicity.

4. Results

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

There were no statistically significant differences for pituitary gland adenomas or carcinomas, pooled or individually.

5. Conclusions

There were no statistically significant differences for pituitary gland adenomas or carcinomas, pooled or individually.

Appendices

A1 Statistical Tables

Table 1. Neoplasms by Body System for Interim Sacrifice Females Bisphenol-A Stop Dose Arm							
System and Neoplasm		***Treatment (ug/kg)***					
Lesion	***Statistic***	***Control***	***2.5***	***25***	***250***	***2500***	***25000***
Endocrine System							
Pituitary Gland * Carcinoma or Adenoma,Pars Distalis	Simple Incidence	0/20 (0.0%)	0/22 (0.0%)	2/20 (10.0%)	0/22 (0.0%)	0/20 (0.0%)	0/22 (0.0%)
	Terminal Incidence	0/20 (0.0%)	0/22 (0.0%)	2/20 (10.0%)	0/22 (0.0%)	0/20 (0.0%)	0/20 (0.0%)
	Time-to-First	----	----	364 (T)	----	----	----
	CAFE P-Value	0.408N		0.244			

P-values for dose trend are presented in the “Control” column.
N indicates a negative trend or negative treatment comparison to control with corresponding lower-tail p-values.