

APPENDIX XVIII

Statistical Analysis of Organ Weights – Females and Males

Statistical Report

Project #: E02186.01
Project Title: Effect of oxybenzone on fertility and early embryonic development in Sprague-Dawley rats (Segment I)
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Task: Statistical Analysis of Organ Weight
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Statistical Analysis of Organ Weight Data

1. Objectives

1.1 Project Objectives

The objective of the study is to examine the reproductive toxicity of oxybenzone in male and female rats and is designed to focus specifically on fertility and early embryonic development to implantation [ICH Guideline S5(R2) 4.1.1]. An additional objective is to compare the results of a typical Segment I, II, III study design with results from a modified one-generation study proposed by the NTP.

1.2 Analysis Objectives

The goal of this analysis is to test the effect of oxybenzone treatment on organ weight

2. Experimental Design

A total of 262 rats were to be requested for this study. Of this number 125 male rats were to be requested along with 125 female rats. Males were to be approximately 5-7 weeks old when delivered to the NCTR, and females were to be approximately 9-11 weeks of age when delivered. All males were to be delivered in one shipment, and all females were to be delivered in a separate shipment. After a two week quarantine period the animals were to be weighed and allocated to the study.

The test article in this study is 2-hydroxy-4-methoxybenzophenone (synonyms: HMB, benzophenone-3, oxybenzone). The animals were to be divided into five treatment groups with 25 male and 25 female rats assigned to each group. The treatment groups were to be four oxybenzone dose levels 0 ppm (control), 3000 ppm, 10,000 ppm, and 30,000 ppm and one estrogen ethinyl estradiol (EE₂) 0.05 ppm treatment.

Males were to be dosed for 10 weeks and females for approximately 2 weeks prior to mating. Dosing was to continue until gestation day (GD) 6 for all animals. From GD 6 to GD 15, dams were to receive control chow. All dams were to be sacrificed on GD 15; males were to be sacrificed soon after breeding (approximately GD 6).

All animals were to be housed in pairs in cages prior to breeding. For breeding, males and females were to be housed one male: one female for up to 15 days or until animals have mated. Males and females were to be housed individually upon indication of mating (GD 0) until the time of sacrifice.

Organs weight data were to include adrenal glands, liver, kidneys and the thyroid gland, reproductive tissues from males (testis, epididymis, dorsolateral and ventral prostate, seminal vesicles with coagulating glands, preputial glands, paired Cowper's glands [bulbourethral gland], levator ani bulbocavernosus muscle complex [LABC]), and reproductive tissue from females (ovaries).

3. Statistical Method

Treatment group means of organ weight were analyzed for males and for pregnant females with known GD 6 (end of dosing). Pairwise comparisons of means were performed using contrasts within a one-way analysis of variance (ANOCOVA) to test for treatment effect with covariate receiving weight for females and males separately. Test of trend, increasing treatment effect with increasing dose, was performed for the oxybenzone and control groups. Comparisons of treatment groups to control were performed with Dunnett's method for adjusted contrasts. All tests were conducted as two-sided at the 0.05 significance level.

4. Results

Tables are included in Appendix A1.

Exclusions of organ weight are presented in Table 1 by treatment group and carcass id number (CID). Exclusions of breeding pairs are presented in Table 2 by treatment group, UIN, and CID. One breeding pair was not monitored for evidence of mating until the 3rd day of pairing, but was plug positive by day 3. There were 12 breeding pairs with unknown GD 0 due to missing plug dates (sires remained in the breeding cages after GD 0 and continued on dosed chow after GD 6). Exclusions of dams are presented in Table 3 by treatment group, UIN, and CID. There were 4 dams that were dosed through GD 8.

Summary statistics of organ weight are given in Table 4 for females and Table 6 for males. Summary statistics of organ weight relative to receiving weight are given in Table 5 for females and Table 7 for males.

For females, the ANOVA omnibus test results are given in Table 8 for the null hypothesis that all of the control, oxybenzone, and EE₂ treatment means for organ weight are equal. Treatment effect for adrenal gland, liver and paired ovary were significant ($p=0.003$, $=0.003$, and <0.001 , respectively). The covariate receiving weight was significant for liver, kidney and paired ovaries ($p<0.001$, $=0.006$, $=0.005$, respectively).

Comparisons of least squares mean female organ weights are presented in Table 9. For adrenal gland, there was a significant difference compared to the control group for oxybenzone 3,000 ppm ($p=0.042$), with the oxybenzone treatment showing higher mean weight (8.6% greater) compared to control. For paired ovaries, there was a significant difference compared to the control group for oxybenzone 10,000 ppm ($p=0.016$), with the dosed group showing higher mean weight (12.1% greater) compared to control. There was a significant trend for liver, but there were no significant comparisons for any treatment group compared to control.

For males, the ANOVA omnibus test results are given in Table 10 for the null hypothesis that all of the control, oxybenzone, and EE₂ treatment means for organ weight are equal. Treatment effect was significant for liver, paired kidneys, and paired testes ($p<0.001$, <0.001 , and $=0.008$, respectively), and covariate receiving weight was significant for paired epididymis, liver, paired kidneys, LABC, paired seminal vesicles, paired testes,

thyroid gland, and urethra bulbourethral glands ($p=0.001$, <0.001 , <0.001 , $=0.001$, $=0.024$, <0.001 , $=0.015$, $=0.027$).

Comparisons of least squares mean male organ weights are presented in Table 11. For liver and paired kidneys, there were significant trends and differences compared to the control group for oxybenzone 10,000 ppm ($p=0.001$ and $=0.001$, respectively) and oxybenzone 30,000 ppm treatment (both $p<0.001$). Relative to the control group mean weights, oxybenzone 10,000 ppm showed higher mean weights (8.1% greater for liver and 9.9% greater for kidney). Oxybenzone 30,000 ppm also showed higher mean weights than control (18.4% greater for liver and 14.8% greater for kidney). For paired seminal vesicles, there was a significant difference for oxybenzone 10,000 ppm ($p=0.049$), with the dosed group showing 12.4% higher mean compared to control. The EE₂ 0.05 ppm differed significantly from the control group for liver ($p=0.022$), with the dosed group showing higher mean relative to the control (7.5% greater). There were significant trends for prostate ventral lobe and paired testes, but no significant pairwise differences for any oxybenzone treatment compared to control.

5. Conclusions

For females, there was a significant difference for adrenal gland for oxybenzone 3,000 ppm compared to the control group ($p=0.042$), with the oxybenzone treatment showing higher mean weight compared to control. For paired ovaries, there was a significant difference compared to the control group for oxybenzone 10,000 ppm ($p=0.016$), with the dosed group showing higher mean weight compared to control.

For males, there were significant differences for oxybenzone 10,000 ppm and oxybenzone 30,000 ppm compared to the control group for liver and kidney, with the dosed treatments showing higher mean weights relative to the control group. For paired seminal vesicles, there was a significant difference for oxybenzone 10,000 ppm, with the dosed group showing higher mean weight compared to control. The EE₂ 0.05 ppm group differed significantly from control for liver, with the dosed group showing higher means relative to control.

Appendices

A1 Statistical Tables

<i>Table 1. Organ Weight Exclusions</i>			
<i>Treatment</i>	<i>Organ (Site)</i>	<i>CID</i>	<i>Comment</i>
CTRL	Adrenal Gland	21860200	Reweighed adrenal glands at post fixed because the weight appeared to be incorrect at the day of necropsy. SW 04-30-13
OXY 3,000	Ovary (Right)	21860200	Cyst attached. KC 04-30-13
	Adrenal Gland	21860200	Weighed after put in fixative. KC 05-20-13
OXY 30,000	Kidney (Left)	21860200	Weighed after put in fixative. KC 05-20-13
	Urethra Bulbourethral Glands	21860200	Weighed after put in fixative. KC 05-20-13

<i>Table 2. Breeding Pairs Exclusions</i>					
<i>Exclusion</i>	<i>Treatment (ppm)</i>	<i>Dam UIN</i>	<i>Dam CID</i>	<i>Sire UIN</i>	<i>Sire CID</i>
Missed VSSE	CTRL	5A000002607	21860200297	5A000002496	21860200004
		5A000002639	21860200250	5A000002528	21860200005
	OXY 10,000	5A000002579	21860200219	5A000002436	21860200063
		5A000002630	21860200218	5A000002437	21860200017
		5A000002636	21860200258	5A000002483	21860200102
		5A000002648	21860200220	5A000002549	21860200064
		5A000002653	21860200260	5A000002487	21860200062
		5A000002580	21860200227	5A000002489	21860200081
		5A000002600	21860200245	5A000002538	21860200087
	5A000002652	21860200244	5A000002516	21860200047	
	5A000002678	21860200230	5A000002445	21860200043	
	EE2 0.05	5A000002661	21860200240	5A000002526	21860200078
	Plug Monitor	CTRL	5A000002671	21860200256	5A000002448

<i>Table 3. Dam Exclusions</i>			
<i>Exclusion</i>	<i>Treatment (ppm)</i>	<i>Dam UIN</i>	<i>Dam CID</i>
Stop Dose Deviation	CTRL	5A000002650	21860200204
	OXY 3,000	5A000002664	21860200216
	OXY 10,000	5A000002658	21860200304
	EE2 0.05	5A000002667	21860200280

Table 4. Summary Statistics of Organ Weight (g) for Females

<i>Treatment (ppm)</i>																
		<i>CTRL</i>			<i>OXY 3,000</i>			<i>OXY 10,000</i>			<i>OXY 30,000</i>			<i>EE2 0.05</i>		
<i>Organ</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>	
Adrenal Gl	11	0.059	0.002	18	0.064	0.002	18	0.060	0.001	17	0.060	0.001	19	0.056	0.001	
Liver	12	12.10	0.30	18	11.42	0.21	18	11.90	0.24	17	11.87	0.15	19	11.58	0.16	
Kidney Left	12	0.849	0.014	18	0.857	0.012	18	0.865	0.012	17	0.835	0.010	19	0.832	0.009	
Kidney Right	12	0.887	0.018	18	0.868	0.011	18	0.879	0.011	17	0.846	0.009	19	0.838	0.011	
Kidney Paired	12	1.736	0.031	18	1.725	0.020	18	1.744	0.021	17	1.681	0.017	19	1.670	0.016	
Ovary Left	12	0.058	0.003	18	0.062	0.003	18	0.063	0.003	17	0.050	0.003	19	0.045	0.002	
Ovary Right	12	0.057	0.004	18	0.062	0.002	18	0.062	0.002	17	0.056	0.003	19	0.049	0.002	
Ovary Paired	12	0.116	0.004	18	0.123	0.003	18	0.125	0.003	17	0.106	0.003	19	0.094	0.002	
Thyroid Gl	12	0.023	0.002	18	0.026	0.001	18	0.024	0.002	17	0.022	0.001	19	0.023	0.001	
Receiving Wt	12	325.7	2.1	18	319.4	2.9	18	316.1	2.0	17	307.1	2.1	19	303.7	2.5	

Table 5. Summary Statistics of Relative Organ to Receiving Weight (mg/g) for Females

<i>Treatment (ppm)</i>																
		<i>CTRL</i>			<i>OXY 3,000</i>			<i>OXY 10,000</i>			<i>OXY 30,000</i>			<i>EE2 0.05</i>		
<i>Organ</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>	
Adrenal Gl	11	0.182	0.005	18	0.201	0.006	18	0.192	0.003	17	0.194	0.004	19	0.185	0.003	
Liver	12	37.16	0.87	18	35.75	0.52	18	37.63	0.61	17	38.64	0.43	19	38.14	0.41	
Kidney Left	12	2.607	0.040	18	2.685	0.035	18	2.736	0.033	17	2.718	0.027	19	2.743	0.037	
Kidney Right	12	2.722	0.044	18	2.722	0.040	18	2.782	0.032	17	2.756	0.027	19	2.764	0.041	
Kidney Paired	12	5.329	0.080	18	5.407	0.067	18	5.518	0.059	17	5.474	0.049	19	5.507	0.070	
Ovary Left	12	0.179	0.008	18	0.194	0.009	18	0.200	0.009	17	0.162	0.009	19	0.148	0.008	
Ovary Right	12	0.175	0.012	18	0.193	0.006	18	0.196	0.008	17	0.183	0.010	19	0.161	0.007	
Ovary Paired	12	0.355	0.011	18	0.387	0.010	18	0.396	0.010	17	0.345	0.009	19	0.309	0.006	
Thyroid Gl	12	0.071	0.005	18	0.081	0.004	18	0.074	0.005	17	0.071	0.004	19	0.075	0.004	

Table 6. Summary Statistics of Organ Weight (g) for Males

<i>Treatment (ppm)</i>															
	<i>CTRL</i>			<i>OXY 3,000</i>			<i>OXY 10,000</i>			<i>OXY 30,000</i>			<i>EE2 0.05</i>		
<i>Organ</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>
Adrenal Gl	22	0.054	0.001	25	0.053	0.001	20	0.052	0.001	20	0.054	0.001	24	0.052	0.001
Epididymis Left	22	0.668	0.009	25	0.651	0.009	20	0.654	0.012	21	0.653	0.009	24	0.672	0.018
Epididymis Right	22	0.669	0.009	25	0.660	0.010	20	0.659	0.010	21	0.655	0.008	24	0.670	0.009
Epididymis Paired	22	1.337	0.017	25	1.311	0.016	20	1.313	0.020	21	1.308	0.015	24	1.342	0.024
Liver	22	14.40	0.33	25	13.95	0.30	20	15.21	0.37	21	15.54	0.35	24	13.75	0.26
Kidney Left	22	1.236	0.025	25	1.265	0.018	20	1.343	0.033	20	1.334	0.031	24	1.192	0.021
Kidney Right	22	1.280	0.026	25	1.273	0.015	20	1.371	0.035	21	1.352	0.037	24	1.204	0.022
Kidney Paired	22	2.516	0.050	25	2.537	0.032	20	2.714	0.066	20	2.690	0.066	24	2.396	0.041
LABC	22	1.157	0.028	25	1.192	0.018	20	1.223	0.028	21	1.110	0.026	24	1.121	0.019
Preputial Gl	22	0.153	0.009	25	0.165	0.019	20	0.145	0.010	21	0.162	0.011	24	0.178	0.012
Pros- Dors/Lat	22	0.485	0.021	25	0.464	0.018	20	0.457	0.018	21	0.421	0.012	24	0.444	0.019
Pros- Ven Lobe	22	0.709	0.025	25	0.658	0.026	20	0.669	0.030	21	0.592	0.025	24	0.633	0.025
SemVes Left	22	0.663	0.022	25	0.652	0.024	20	0.741	0.030	21	0.646	0.022	24	0.692	0.023
SemVes Right	22	0.628	0.020	25	0.621	0.024	20	0.694	0.038	21	0.625	0.024	24	0.624	0.024
SemVes Paired	22	1.292	0.039	25	1.274	0.042	20	1.435	0.054	21	1.271	0.040	24	1.316	0.043
Testes Left	22	1.941	0.026	25	1.894	0.022	20	1.887	0.028	21	1.901	0.029	24	1.948	0.019
Testes Right	22	1.938	0.026	25	1.892	0.024	20	1.919	0.028	21	1.952	0.053	24	1.937	0.023
Testes Paired	22	3.879	0.050	25	3.785	0.045	20	3.806	0.053	21	3.853	0.079	24	3.885	0.041
Thyroid Gl	22	0.025	0.001	25	0.025	0.001	20	0.025	0.001	21	0.025	0.001	24	0.024	0.001
Urethra	22	0.096	0.002	25	0.096	0.003	20	0.093	0.003	20	0.091	0.003	24	0.088	0.002
Receiving Wt	22	412.7	5.8	25	403.5	4.3	20	406.2	6.1	21	382.8	4.0	24	376.5	3.8

Table 7. Summary Statistics of Relative Organ to Receiving Weight (mg/g) for Males

Organ	Treatment (ppm)														
	CTRL			OXY 3,000			OXY 10,000			OXY 30,000			EE2 0.05		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Adrenal Gl	22	0.131	0.004	25	0.131	0.003	20	0.129	0.003	20	0.142	0.004	24	0.140	0.003
Epididymis Left	22	1.623	0.024	25	1.618	0.025	20	1.614	0.033	21	1.709	0.028	24	1.789	0.050
Epididymis Right	22	1.623	0.021	25	1.636	0.022	20	1.627	0.025	21	1.713	0.027	24	1.783	0.026
Epididymis Paired	22	3.247	0.042	25	3.254	0.043	20	3.241	0.055	21	3.422	0.050	24	3.571	0.068
Liver	22	34.84	0.48	25	34.54	0.56	20	37.46	0.76	21	40.56	0.72	24	36.48	0.45
Kidney Left	22	2.995	0.047	25	3.137	0.042	20	3.303	0.052	20	3.480	0.067	24	3.167	0.047
Kidney Right	22	3.102	0.046	25	3.158	0.038	20	3.372	0.058	21	3.531	0.085	24	3.201	0.051
Kidney Paired	22	6.097	0.089	25	6.295	0.077	20	6.675	0.108	20	7.020	0.145	24	6.368	0.095
LABC	22	2.805	0.056	25	2.959	0.050	20	3.014	0.059	21	2.906	0.077	24	2.985	0.061
Preputial Gl	22	0.371	0.023	25	0.410	0.044	20	0.357	0.025	21	0.426	0.029	24	0.471	0.031
Pros- Dors/Lat	22	1.181	0.055	25	1.150	0.043	20	1.126	0.044	21	1.099	0.030	24	1.182	0.052
Pros- Ven Lobe	22	1.722	0.062	25	1.636	0.067	20	1.643	0.067	21	1.546	0.062	24	1.690	0.072
SemVes Left	22	1.609	0.051	25	1.619	0.058	20	1.824	0.067	21	1.692	0.061	24	1.845	0.065
SemVes Right	22	1.526	0.049	25	1.544	0.063	20	1.706	0.090	21	1.634	0.063	24	1.657	0.061
SemVes Paired	22	3.135	0.094	25	3.163	0.108	20	3.530	0.120	21	3.326	0.108	24	3.502	0.114
Testes Left	22	4.713	0.062	25	4.700	0.055	20	4.657	0.076	21	4.967	0.063	24	5.184	0.070
Testes Right	22	4.704	0.061	25	4.694	0.060	20	4.737	0.078	21	5.091	0.103	24	5.156	0.074
Testes Paired	22	9.417	0.118	25	9.394	0.111	20	9.393	0.147	21	10.058	0.150	24	10.340	0.142
Thyroid Gl	22	0.062	0.002	25	0.063	0.003	20	0.062	0.003	21	0.065	0.002	24	0.064	0.003
Urethra	22	0.233	0.006	25	0.237	0.007	20	0.229	0.006	20	0.239	0.007	24	0.235	0.006

Table 8. ANCOVA Results for Female Organ Weight¹

<i>Organ</i>	<i>Effect</i>	<i>NumDF</i>	<i>DenDF</i>	<i>Fvalue</i>	<i>P</i>
Adrenal Gland	Receiving Wt	1	77	0.124	0.726
	Treatment	4	77	4.387	0.003
Liver	Receiving Wt	1	78	35.123	<.001
	Treatment	4	78	4.424	0.003
Kidney Paired	Receiving Wt	1	78	8.073	0.006
	Treatment	4	78	0.746	0.564
Ovary Paired	Receiving Wt	1	78	8.379	0.005
	Treatment	4	78	11.824	<.001
Thyroid Gland	Receiving Wt	1	78	0.007	0.935
	Treatment	4	78	1.141	0.343

Table 9. ANCOVA Comparisons of Least Squares Mean Female Organ Weights Across Treatment Groups

<i>Organ</i>	<i>Treatment (ppm)</i>																		
	<i>Control</i>				<i>OXY 3,000</i>				<i>OXY 10,000</i>				<i>OXY 30,000</i>				<i>EE2 0.05</i>		
	<i>Mean</i>	<i>SE</i>	<i>Pvalue</i>	<i>Pct</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>
Adrenal Gland	0.059	0.002	0.490	0.064	0.001	108.6	0.042	0.060	0.001	102.4	0.855	0.060	0.001	101.4	0.984	0.057	0.001	95.8	0.613
Liver	11.52	0.229	0.002	11.14	0.175	96.7	0.399	11.78	0.170	102.3	0.707	12.17	0.181	105.7	0.104	12.05	0.183	104.7	0.245
Kidney Paired	1.705	0.025	0.701	1.710	0.019	100.3	0.999	1.738	0.019	101.9	0.619	1.698	0.020	99.6	0.998	1.696	0.020	99.5	0.996
Ovary Paired	0.111	0.004	0.113	0.121	0.003	109.4	0.072	0.124	0.003	112.1	0.016	0.109	0.003	98.1	0.977	0.098	0.003	88.2	0.050
Thyroid Gland	0.023	0.002	0.177	0.026	0.001	110.1	0.534	0.024	0.001	101.3	1.000	0.022	0.001	93.2	0.865	0.023	0.001	97.4	0.996

1. All p-values and % are relative to the control group, except p-values for the linear trend are presented under the control group.

Table 10. ANOCOVA Results for Male Organ Weight

Organ	Effect	NumDF	DenDF	Fvalue	P
Adrenal Gland	Receiving Wt	1	105	3.181	0.077
	Treatment	4	105	0.606	0.659
Epididymis Paired	Receiving Wt	1	106	12.447	0.001
	Treatment	4	106	1.954	0.107
Liver	Receiving Wt	1	106	96.418	<.001
	Treatment	4	106	17.096	<.001
Kidney Paired	Receiving Wt	1	105	56.333	<.001
	Treatment	4	105	10.712	<.001
LABC	Receiving Wt	1	106	10.752	0.001
	Treatment	4	106	1.989	0.101
Preputial Gland	Receiving Wt	1	106	0.715	0.400
	Treatment	4	106	1.061	0.380
Pros- Dors/Lat	Receiving Wt	1	106	2.713	0.103
	Treatment	4	106	0.739	0.568
Pros- Ven Lobe	Receiving Wt	1	106	1.563	0.214
	Treatment	4	106	1.404	0.238
SemVes Paired	Receiving Wt	1	106	5.249	0.024
	Treatment	4	106	2.340	0.060
Testes Paired	Receiving Wt	1	106	26.215	<.001
	Treatment	4	106	3.641	0.008
Thyroid Gland	Receiving Wt	1	106	6.100	0.015
	Treatment	4	106	0.108	0.980
Urethra Bulboureth Glands	Receiving Wt	1	105	5.059	0.027
	Treatment	4	105	0.414	0.798

Table 11. ANCOVA Comparisons of Least Squares Mean Male Organ Weights Across Treatment Groups

<i>Organ</i>	<i>Treatment (ppm)</i>																		
	<i>Control</i>			<i>OXY 3,000</i>				<i>OXY 10,000</i>				<i>OXY 30,000</i>				<i>EE2 0.05</i>			
	<i>Mean</i>	<i>SE</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>	<i>Mean</i>	<i>SE</i>	<i>Pct</i>	<i>Pvalue</i>
Adrenal Gland	0.053	0.001	0.253	0.052	0.001	98.5	0.975	0.052	0.001	97.7	0.912	0.055	0.001	103.0	0.832	0.053	0.001	100.3	1.000
Epididymis Paired	1.316	0.019	0.531	1.302	0.017	98.9	0.944	1.300	0.019	98.8	0.936	1.325	0.019	100.7	0.993	1.368	0.019	103.9	0.211
Liver	13.63	0.248	<.001	13.61	0.223	99.8	1.000	14.74	0.251	108.1	0.006	16.14	0.248	118.4	<.001	14.65	0.243	107.5	0.022
Kidney Paired	2.415	0.043	<.001	2.493	0.039	103.2	0.452	2.653	0.044	109.9	0.001	2.772	0.045	114.8	<.001	2.518	0.043	104.3	0.308
LABC	1.132	0.024	0.409	1.181	0.022	104.3	0.354	1.208	0.025	106.7	0.082	1.130	0.024	99.7	1.000	1.151	0.024	101.6	0.962
Preputial Gland	0.149	0.014	0.549	0.164	0.013	110.0	0.834	0.142	0.014	95.6	0.991	0.165	0.014	111.1	0.840	0.182	0.014	122.3	0.323
Pros- Dors/Lat	0.475	0.019	0.109	0.460	0.017	96.8	0.929	0.451	0.019	95.0	0.772	0.429	0.019	90.3	0.293	0.456	0.019	96.0	0.907
Pros- Ven Lobe	0.698	0.028	0.031	0.653	0.025	93.6	0.550	0.662	0.028	94.9	0.755	0.601	0.028	86.2	0.067	0.646	0.027	92.7	0.538
SemVes Paired	1.259	0.046	0.576	1.259	0.041	100.0	1.000	1.415	0.046	112.4	0.049	1.297	0.046	103.1	0.941	1.355	0.045	107.7	0.413
Testes Paired	3.796	0.052	0.029	3.748	0.046	98.7	0.887	3.755	0.052	98.9	0.942	3.919	0.052	103.3	0.299	3.983	0.051	104.9	0.054
Thyroid Gland	0.025	0.001	0.625	0.025	0.001	102.2	0.988	0.025	0.001	100.1	1.000	0.025	0.001	103.7	0.948	0.025	0.001	102.0	0.994
Urethra Bulbourethral Glands	0.094	0.003	0.709	0.095	0.002	100.7	0.999	0.092	0.003	97.3	0.898	0.093	0.003	98.8	0.996	0.091	0.003	96.4	0.811

1. All p-values and % are relative to the control group, except p-values for the linear trend are presented under the control group.

A2 Data

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

Statistical Analysis of Organ Weight Data – QC

1. Data Verification

The extraction of the data into SAS was verified by the reviewer, Paul Felton, 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, and by independent verification of the results.

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 presented 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 independent verification of the numerical results.

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.