E02186.01 Technical Report Tables

TABLE OF CONTENTS: E02186.01 TECHINCAL REPORT SUMMARY TABLES

TABLE 1
Experimental Design and Materials and Methods for the Fertility and Embryonic Development Feed Study of Oxybenzone

Experimental Design and Materials & Methods	
Study Information	
Study Laboratory	National Center for Toxicological Research (NCTR), 3900 NCTR Road, Jefferson, AR 72079
Test Article	Oxybenzone (OXY)
Synonyms:	2-hydroxy-4-methoxybenzophenone, HMB, benzophenone-3, (2-hydroxy-4-methoxyphenyl)-phenylmethanone
CAS No.	131-57-7
Purity	>99%
Supplier	Ivy Fine Chemicals, Cherry Hill, NJ [catalog number: HH13-026; lot #: 1F100604]
Control Article	Ethinyl Estradiol (EE2)
Synonyms:	17α-ethynylestradiol
CAS No.	57-63-6
Purity	≥98%
Supplier	Sigma-Aldrich, St. Louis, MO [catalog number: E4876; lot# 071M14392V]
Dates of Study Initiation and Completion	Protocol Approved: April 6, 2012 In-Life Males Initiation: January 28, 2013 Completion: May 23, 2013 In-Life Females Initiation: March 8, 2013 Completion: May 29, 2013 Final Report Signed: June 23, 2016
Animals and Animal Maintenance	
Species/Strain/Substrain	Rat/Sprague-Dawley/Harlan
Animal Source	Harlan Industries (Indianapolis, IN)
Receiving Dates	Males: January 14, 2013 Females: February 25, 2013
Dates of First Exposure	Males: January 28, 2013 Females: March 25, 2013

Experimental Design and Materials & Methods	
Age and Weight of Animals at Allocation	Male animals were between 7-9 weeks old at the time of allocation while females were between 11-13 weeks. At allocation the males and females weighed between 200-250 grams.
Acclimation Time before Start of Test	Males – 3 days after allocation to study. Females – 17 days after allocation to study; vaginal cytology monitored for 14 days prior to the start of test article. Males and females were placed on a soy- and alfalfa-free diet (Purina 5K96) upon arrival at the NCTR.
Method of Allocation	Animals were allocated to exposure groups by a weight-ranked randomization method such that the mean initial weight of each group was approximately the same.
Animal Identification	Tail tattoo.
Method of Euthanasia	Carbon dioxide asphyxiation.
Feed	Irradiated Purina 5K96 chow (Test Diets, Purina Mills, Inc., St. Louis, MO), available *ad libitum*. Each lot was analyzed by the Chemistry Support Group, Division of Biochemical Toxicology, NCTR, Jefferson, AR.
Water	Millipore®-filtered tap water (Jefferson, AR municipal supply) via water bottles, available *ad libitum*.
Animals per Cage	Animals were housed in pairs upon arrival at the study laboratory. Females were paired housed until mating; males were separated and singly housed approximately 48 hours prior to mating. For mating, one male and one female were placed together for up to 15 days or until mating occurred. Animals were separated and housed individually upon evidence of mating (sperm positive lavage or vaginal plug detection) or if after 15 days of cohabitation no evidence of mating was observed until sacrifice.
Cages	Solid-bottom polysulfone cages (Allentown Caging Equipment Co., Allentown, NJ), changed at least once weekly.
Bedding	Irradiated heat-treated hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed at least once weekly.
Cage Bonnets	Microisolator tops (Lab Products, Inc., Maywood, NJ), changed every three weeks.
Racks	Metal animal cage racks (Allentown Caging Equipment Co., Allentown, NJ), changed every three weeks.
Animal Room Environment	Temperature: 23°C ± 3°C Relative humidity: 50% ± 20% Room fluorescent light: 12 hours/day Room air changes: at least 10/hour

Experimental Design and Materials & Methods	
Sentinel Animals/Microbiological Surveillance	Sentinel animals (a total of eight) were maintained in the animal rooms utilized in the study and were evaluated during the course of the study and at study completion. Animal room supplies (food, water, bedding) and swabs from the animal rooms were also evaluated. An additional four animals (two per shipment) were ordered for microbiology surveillance. These animals were tested upon arrival.
Experimental Design	
Size of Study Groups	Twenty-five rats per sex per treatment group.
Doses/Route of Exposure	Oxybenzone (OXY): 0; 3,000; 10,000; 30,000 ppm in feed (5K96), available *ad libitum.* Ethinyl estradiol (EE2): 0.05 ppm in feed (5K96), available *ad libitum*.
Duration of Exposure*	*Duration of exposure based on positive vaginal lavage or detection of a vaginal plug. *Male Ranges:* OXY 0 (CTRL) 78 days – 104 days OXY 3,000 79 days – 104 days OXY 10,000 80 days – 108 days OXY 30,000 76 days – 113 days EE2 0.05 79 days – 112 days *Female Ranges:* OXY 0 (CTRL) 22 days – 48 days OXY 3,000 23 days – 48 days OXY 10,000 24 days – 52 days OXY 30,000 20 days – 57 days EE2 0.05 23 days – 56 days
Type and Frequency of Observations	Animals were observed twice daily for morbidity and mortality; clinical signs were recorded twice weekly. Body weights of males were recorded twice per week from the day of allocation until the determination of pregnancy (GD 0). The weights of males were recorded on GD 0, GD 6 (end of dosing) and at sacrifice. Body weights of females were recorded twice per week from the day of allocation until the beginning of pregnancy (GD 0). Body weights of females were recorded on GD 0, GD 6 (end of dosing), GD 10 and GD 15 (sacrifice). Food consumption was measured twice weekly beginning at the time of allocation until mating. Food consumption was not measured during the mating period. Food consumption measurements resumed at GD 0 and continued through GD 6 for both males and females with measurements occurring on GD 0 and GD 6. Consumption was monitored until GD 15 for females. Water consumption was not measured. During the mating period, vaginal lavage was performed every morning to detect the presence of sperm in the vagina to establish the date of mating/pregnancy. A sperm positive lavage or a vaginal plug preventing lavage was considered evidence of mating and designated as GD 0. Vaginal lavages were performed for up to 14 days during the mating period.

Experimental Design and Materials & Methods	
Necropsy	At sacrifice animals underwent a gross examination and complete necropsy of the thoracic and abdominal cavities. Any gross lesions, if identified, were collected and processed for histopathology. Organ weights for the testis (separate), epididymis (separate), dorsolateral and ventral prostate (separate after fixation), seminal vesicles with coagulating glands, paired preputial glands, paired Cowper's glands, and the levator ani bulbocavernosus muscle complex were obtained from the males. Organ weights for the uterus with the right ovary, vagina and cervix attached were obtained from the females. The number and status of each implantation site was recorded. For any female that appeared non-pregnant, the uterus was stained with 10% ammonium sulfide. Following examination of the uterus, the right ovary was removed and weighed separately; weights were also separately recorded for the left ovary. Ovaries were retained for counting of corpora lutea and fixed for follicle counts if triggered. Organ weights for the adrenal glands (paired), liver, kidneys (separate), thyroid gland (weighed following fixation) and any gross lesions were obtained from both male and female animals. The mammary glands, pituitary gland and any retained nipples, if present, were also collected, but not weighed. Blood samples for hematological and clinical chemistry analysis were collected from 10 randomly selected male and 10 pregnant female animals in each treatment group. Hormone levels were also assessed in the 10 randomly selected males.
Histopathology	Histopathology was performed on any gross lesion detected throughout the study. To serve as a reference for gross lesions, all tissues from one male and one female per dose group were collected and processed to slides. Histopathology was performed on the tissues of the males and females in the OXY 30,000 ppm, CTRL and the EE2 0.05 ppm treatment groups; other dose groups were evaluated only if triggered. For males, histopathology analysis was conducted on the right testis, right epididymis, dorsolateral prostate, ventral prostate, seminal vesicles with coagulating glands, retained nipples (if noted), mammary glands, adrenal glands, pituitary glands and the thyroid gland. Histopathology on the preputial glands, paired Cowper's glands, and the levator ani bulbocavernosus complex was at the discretion of the Study Pathologist and/or Study Director. Histopathological analysis for females included the mammary glands. Histopathology of the ovaries, the uterus (with attached vagina and cervix), adrenal, pituitary and thyroid glands from the females was at the discretion of the Study Pathologist and/or Study Director. The liver and kidneys from both the males and females were processed to block and held; histopathology was at the discretion of the Study Pathologist and/or Study Director.

Experimental Design and Materials & Methods	
Sperm Analysis and Vaginal Cytology	At sacrifice, sperm samples were collected from 10 randomly identified males for evaluation. The following parameters were evaluated: sperm motility, epididymal sperm counts, testicular spermatid head counts and sperm morphology. Vaginal samples were collected for 14 consecutive days starting three days after allocation to study and for 14 consecutive days beginning at the time of dosing for vaginal cytology evaluations. The evaluations included: the percentage of time spent in the stages of the estrus cycle, percentages of abnormal cycles of estrus, diestrus, proestrus and the sum of the abnormal cycles and estrus cycle length.
Test Article Vehicle Mixture - Oxybenzone	
Mixture Preparation	Weighed amounts of oxybenzone were mixed with Purina 5K96 chow on an as needed basis. Doses were prepared by the Diet Preparation Group, Priority One Services, NCTR, Jefferson, AR.
Stability	Oxybenzone was found to be stable in Purina 5K96 chow through seven weeks[1] at refrigerated temperature in E0217801 [Dose-Finding Oxybenzone – NTP; non-GLP].
Storage Conditions of Test Article	Stored in the original containers(s) at room temperature.
Storage Conditions of Dose Formulations	Dose formulations were stored in stainless steel cans secured with tie-downs at 4°C ± 2°C.
Control Article Vehicle Mixture – Ethinyl Estradiol	
Mixture Preparation	A concentrated solution of ethinyl estradiol was prepared in 95% ethanol by the Chemistry Support Group, Division of Biochemical Toxicology, NCTR, Jefferson, AR and provided to the Diet Preparation Group, Priority One Services, NCTR, Jefferson, AR for preparation of the dose formulations. Dose formulations were prepared on an as needed basis by mixing the test article with 5K96 chow under a vacuum.
Stability	Ethinyl estradiol was confirmed to be stable in Purina 5K96 chow for at least 24 weeks at refrigerated temperature or for up to 16 days under simulated animal room conditions (NTP, 2010a; NTP 2010b).
Storage Conditions of Control Article	Stored in the original containers(s) at room temperature.
Storage Conditions of Control Article Dose Formulations	Dose formulations were stored in stainless steel cans secured with tie-downs at 4°C ± 2°C.

[1]Stability at the time the protocol was approved was six weeks. Refer to the Analytical Chemistry Report (Appendix IV) for data supporting stability of seven weeks.

TABLE 2
Pre-Mating Body Weights (g) of Female Rats Administered Dietary Oxybenzone[a,b]

Day	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
1	242.4 ± 1.2 (25)	244.0 ± 1.2 (25)	242.0 ± 1.2 (25)	242.9 ± 1.2 (25)	242.9 ± 1.2 (25)
5**	246.1 ± 1.3 (25)	246.6 ± 1.3 (25)	239.3 ± 1.3** (25)	235.0 ± 1.3** (25)	229.9 ± 1.3** (25)
9**	249.6 ± 1.4 (25)	247.8 ± 1.4 (25)	243.7 ± 1.4* (25)	236.5 ± 1.4** (25)	229.8 ± 1.4** (25)
12**	252.7 ± 1.6 (25)	251.0 ± 1.6 (25)	247.7 ± 1.6 (25)	237.8 ± 1.6** (25)	233.0 ± 1.6** (25)
1-12**	247.7 ± 1.1 (25)	247.3 ± 1.1 (25)	243.2 ± 1.1* (25)	238.1 ± 1.1** (25)	233.9 ± 1.1** (25)

ANOCOVA results: Treatment, p = < 0.001; Day, p = < 0.001; Treatment x Day, p = < 0.001; Baseline weight, p = < 0.001.
[a]Females were treated with dietary oxybenzone or ethinyl estradiol for at least 2 weeks prior to mating.
[b]Mean body weight (g) ± S.E.M. Numbers in parentheses indicate number of females per treatment group.
Asterisks (*) adjacent to day in shaded cells indicate significant trends in least square mean comparisons of pre-mating female body weights; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences on the corresponding treatment days to controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p \leq 0.001$.

TABLE 3
Pre-Mating Body Weights (g) of Male Rats Administered Dietary Oxybenzone[a,b]

Week	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
1*	260.3 ± 1.7 (25)	256.9 ± 1.7 (25)	255.5 ± 1.7 (25)	239.2 ± 1.7* (25)	251.5 ± 1.7* (25)
2*	280.7 ± 2.1 (25)	276.0 ± 2.1 (25)	277.5 ± 2.1 (25)	266.4 ± 2.1* (25)	262.9 ± 2.1* (25)
3*	302.3 ± 2.3 (25)	298.0 ± 2.3 (25)	299.0 ± 2.3 (25)	290.0 ± 2.3* (25)	280.6 ± 2.3* (25)
4*	321.6 ± 2.8 (25)	318.4 ± 2.8 (25)	314.7 ± 2.8 (25)	305.4 ± 2.8* (25)	295.3 ± 2.8* (25)
5*	335.0 ± 2.9 (25)	331.1 ± 2.9 (25)	328.1 ± 2.9 (25)	314.3 ± 2.9* (25)	306.3 ± 2.9* (25)
6*	346.6± 3.2 (25)	341.6 ± 3.2 (25)	340.7 ± 3.2 (25)	326.7 ± 3.2* (25)	314.9 ± 3.2* (25)
7*	358.7 ± 3.3 (25)	354.6 ± 3.3 (25)	352.9 ± 3.3 (25)	337.1 ± 3.3* (25)	324.7 ± 3.3* (25)
8*	366.6 ± 3.4 (25)	362.4 ± 3.4 (25)	360.8 ± 3.4 (25)	341.6 ± 3.4* (25)	329.1 ± 3.4* (25)
9*	378.5 ± 3.6 (25)	370.4 ± 3.6 (25)	368.1 ± 3.6 (25)	349.2 ± 3.6* (25)	335.8 ± 3.6* (25)
10*	383.5 ± 3.7 (25)	376.4 ± 3.7 (25)	374.3 ± 3.7 (25)	354.4 ± 3.7* (25)	342.3 ± 3.7* (25)
1-10*	333.4 ± 2.5 (25)	328.6 ± 2.5 (25)	327.2 ± 2.5 (25)	312.4 ± 2.5* (25)	304.3 ± 2.5* (25)

ANOCOVA results: Treatment, p = < 0.001; Week, p = < 0.001; Treatment x Week, p = < 0.001; Baseline weight, p = < 0.001.

[a]Males were treated with dietary oxybenzone or ethinyl estradiol for at least 10 weeks prior to mating.

[b]Mean body weight (g) ± S.E.M. Numbers in parentheses indicate number of males per treatment group.

Asterisks (*) adjacent to week in shaded cells indicate significant trends in least square mean comparisons of pre-mating male body weights; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences at the corresponding weekly time point to controls as determined by Dunnett's method for adjusted contrasts. *, p ≤ 0.001.

TABLE 4
Daily Food Consumption (g/animal/day) of Female Rats Administered Dietary Oxybenzone Prior to Mating[a,b,c]

Food Consumption (Treatment Days)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
1-5	18.2 ± 2.3 (13)	18.6 ± 2.3 (13)	17.0 ± 2.3 (13)	20.6 ± 2.3 (13)	13.2 ± 2.3 (13)
6-9**	20.6 ± 1.5 (13)	20.3 ± 1.5 (13)	24.0 ± 1.5 (13)	26.0 ± 1.5* (13)	16.6 ± 1.5 (13)
10-12*	23.0 ± 2.0 (13)	26.1 ± 2.0 (13)	23.4 ± 2.0 (13)	29.7 ± 2.0 (13)	27.4 ± 2.0 (13)
1-12*	20.6 ± 1.5 (13)	21.7 ± 1.5 (13)	21.5 ± 1.5 (13)	25.4 ± 1.5 (13)	19.1 ± 1.5 (13)

[a]Females were fed dosed chow for at least two weeks prior to mating.
[b]Mean daily food consumption (g/animal/day) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of cages; data were collected from 25 animals per treatment group.
[c]ANOVA results: Treatment, $p = 0.047$; Day, $p = <0.001$; Treatment * Day, $p = 0.008$.
Asterisks (*) adjacent to food consumption designation in shaded cells indicate significant trends in least square mean comparisons of female food consumption prior to mating. The EE2 0.05 ppm treatment group was excluded from the analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences from controls at the same treatment days as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$.

TABLE 5
Daily Food Consumption (g/animal/day) of Male Rats Administered Dietary Oxybenzone Prior to Mating[a,b,c]

Food Consumption (Treatment Week)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
1	22.0 ± 0.9 (13)	20.5 ± 0.9 (13)	21.0 ± 0.9 (13)	23.3 ± 0.9 (13)	20.0 ± 0.9 (13)
2**	21.0 ± 1.1 (13)	18.7 ± 1.1 (13)	21.6 ± 1.1 (13)	24.4 ± 1.1 (13)	20.9 ± 1.1 (13)
3**	22.2 ± 1.1 (13)	22.2 ± 1.1 (13)	21.8 ± 1.1 (13)	25.9 ± 1.1* (13)	24.1 ± 1.1 (13)
4	22.7 ± 1.2 (13)	23.4 ± 1.2 (13)	21.6 ± 1.2 (13)	23.8 ± 1.2 (13)	26.1 ± 1.2 (13)
5	23.3 ± 1.5 (13)	24.5 ± 1.5 (13)	21.3 ± 1.5 (13)	21.4 ± 1.5 (13)	27.0 ± 1.5 (13)
6	21.1 ± 1.0 (13)	22.4 ± 1.0 (13)	21.7 ± 1.0 (13)	22.0 ± 1.0 (13)	23.8 ± 1.0 (13)
7	22.8 ± 1.2 (13)	23.1 ± 1.2 (13)	21.3 ± 1.2 (13)	21.8 ± 1.2 (13)	25.4 ± 1.2 (13)
8	20.2 ± 1.1 (13)	22.4 ± 1.1 (13)	20.1 ± 1.1 (13)	20.2 ± 1.1 (13)	22.8 ± 1.1 (13)
9	21.2 ± 1.1 (13)	23.0 ± 1.1 (13)	20.9 ± 1.1 (13)	21.9 ± 1.1 (13)	22.8 ± 1.1 (13)
10	22.4 ± 0.9 (13)	23.1 ± 0.9 (13)	20.5 ± 0.9 (13)	21.4 ± 0.9 (13)	22.7 ± 0.9 (13)
1-10	21.9 ± 0.7 (13)	22.3 ± 0.7 (13)	21.2 ± 0.7 (13)	22.6 ± 0.7 (13)	23.6 ± 0.7 (13)

[a]Males were fed dosed chow for at least 10 weeks prior to mating.
[b]Mean daily food consumption (g/animal/day) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of cages; data were collected from 25 animals per treatment group.
[c]ANOVA results: Treatment, $p = 0.214$; Week, $p = <0.001$; Treatment * Week, $p = 0.005$.
Asterisks (*) adjacent to food consumption designation in shaded cells indicate significant trends in least square mean comparisons of male food consumption. The EE2 0.05 ppm treatment group was excluded from the analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences from controls during the indicated treatment week as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$.

TABLE 6
Estimated Pre-Mating Ingested Doses (mg/kg of body weight/day) of Oxybenzone in Female Rats[a,b,c]

Pre-Mating Dosing Period	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Days 1-12	0.0 ± 0.0	263.5 ± 15.8 [208.9 – 337.3]	856.2 ± 65.0 [713.0 – 1660.1]	3,128.1 ± 276.4 [2,255.7 – 5,615.4]	0.005 ± 0.001 [0.003 – 0.006]

[a]The mean ingested dose for the pre-mating period was calculated by multiplying the dietary concentration of oxybenzone or EE2 by the mean measured amount of food ingested at days 1, 5, 9 and 12 and dividing the result by the mean body weight for the corresponding treatment day. The means for each day were then averaged to determine an approximate mean ingested dose.
[b]Mean dose (mg/kg body weight per day) ± S.E.M.
[c]Numbers in brackets indicate the range of estimated ingested doses; ranges shown are averages of pre-mating day 1, 5, 9 and 12 data from individual animals.

TABLE 7
Estimated Pre-Mating Ingested Doses (mg/kg of body weight/day) of Oxybenzone in Male Rats[a,b,c]

Pre-Mating Dosing Period	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Weeks 1-10	0.0 ± 0.0	205.8 ± 6.1 [180.1 – 338.4]	658.5 ± 30.1 [574.5 – 781.8]	2,213.5 ± 134.2 [1,834.6 – 2,853.0]	0.004 ± 0.000 [0.003 – 0.005]

[a]The mean ingested dose for the pre-mating period was calculated by multiplying the dietary concentration of oxybenzone or EE2 by the mean measured amount of food ingested at weeks 1-10 and dividing the result by the mean body weight for the corresponding week. The means for each week were then averaged to determine an approximate mean ingested dose.
[b]Mean dose (mg/kg body weight per day) ± S.E.M.
[c]Numbers in brackets indicate the range of estimated ingested doses; ranges shown are averages of pre-mating weeks 1-10 data from individual animals.

TABLE 8
Gestational Body Weights (g) of Female Rats Administered Dietary Oxybenzone[a,b,c]

Gestational Day (GD)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
0* **	266.4 ± 4.3 (11)	259.2 ± 3.4 (19)	260.4 ± 3.5 (18)	246.7 ± 3.8** (17)	246.0 ± 3.3*** (20)
6* **	286.0 ± 2.5 (13)	283.8 ± 2.0 (19)	278.8 ± 2.0 (19)	264.3 ± 2.1*** (17)	260.1 ± 1.9*** (20)
10* **	300.2 ± 2.4 (12)	297.6 ± 2.0 (18)	293.3 ± 2.0 (18)	286.9 ± 2.0*** (17)	287.4 ± 1.9*** (19)
15* **	327.1 ± 2.7 (12)	320.9 ± 2.3 (18)	317.7 ± 2.3* (18)	309.3 ± 2.4*** (17)	304.8 ± 2.2*** (19)
0-15* **	294.9 ± 2.2	290.4 ± 1.8	287.6 ± 1.8*	276.8 ± 1.9***	274.6 ± 1.7***

[a]Mean body weight (g) ± S.E.M. Numbers in parentheses indicate number of pregnant females per treatment group.
[b]Detection of sperm by vaginal lavage or the presence of a vaginal plug was considered evidence of mating (GD 0). Females received dosed feed through implantation (GD 6).
[c]Analysis includes a female in the OXY 10,000 ppm treatment group sacrificed on GD 14 and a female in the EE2 0.05 ppm treatment group sacrificed on GD 13. Analysis excluding the weight of these two animals did not result in any differences in conclusions.
ANOVA results: Treatment, $p = < 0.001$; Gestational Day, $p = < 0.001$; Treatment x Gestational Day, $p = < 0.001$.
Asterisks (*) adjacent to gestational day in shaded cells indicate significant trends in least square mean comparisons of gestational body weights; the EE2 0.05 treatment group was excluded from analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences at corresponding gestational days to controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$; ***, $p \leq 0.001$.

TABLE 9
Post-Mating Body Weights of Male Rats Administered Dietary Oxybenzone[a,b,c]

Gestational Day (GD)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
0*	397.6 ± 6.2 (10)	389.1 ± 5.0 (19)	387.8 ± 5.1 (17)	359.2 ± 5.3* (17)	354.3 ± 4.9* (20)
6*	406.9 ± 6.0 (13)	397.0 ± 4.9 (18)	399.8 ± 4.9 (19)	369.4 ± 5.2* (16)	363.2 ± 4.8* (20)
0-6*	402.2 ± 6.0	393.0 ± 4.9	393.8 ± 4.9	364.3 ± 5.2*	358.8 ± 4.8*

[a]Mean body weight (g) ± S.E.M. Numbers in parentheses indicate number of males in breeding pairs with a known mating date (GD 0) that resulted in pregnancy. Seven males had missing body weights at either GD 0 or GD 6 of the female's pregnancy.
[b]Males were fed dosed chow for at least 10 weeks prior to mating through implantation (GD 6) of the female's pregnancy.
[c]ANOVA results: Treatment, p = <0.001; Gestational Day, p = <0.001; Treatment * Gestational Day, p = 0.592.
Asterisks (*) adjacent to gestational day in shaded cells indicate significant trends in least square mean comparisons of post-mating male body weights. The EE2 0.05 ppm treatment group was excluded from the analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences at corresponding gestational days to controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.001$.

TABLE 10
Daily Gestational Food Consumption (g/animal/day) of Female Rats Administered Dietary Oxybenzone[a,b,c]

Food Consumption (Interval Days)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
GD 0-6*	25.9 ± 3.2 (13)	25.6 ± 2.7 (19)	25.8 ± 2.7 (19)	44.9 ± 2.8* (17)	51.3 ± 2.6* (20)
GD 7-15	24.4 ± 1.6 (12)	23.7 ± 1.3 (18)	25.7 ± 1.3 (18)	27.2 ± 1.4 (17)	25.5 ± 1.3 (19)
GD 0-15*	25.2 ± 2.1	24.6 ± 1.7	25.7 ± 1.7	36.0 ± 1.8*	38.4 ± 1.7*

[a]Mean daily food consumption (g/animal/day) ± S.E.M. Numbers in parentheses indicate number of pregnant females per treatment group.
[b]Females were fed dosed chow for at least two weeks prior to mating. Dosing was continuous through implantation (GD 6).
[c]ANOVA results: Treatment, p = <0.001; Interval, p = <0.001; Treatment * Interval, p = <0.001.
Asterisks (*) adjacent to food consumption designation in shaded cells indicate significant trends in least square mean comparisons of female food consumption during gestation. The EE2 0.05 ppm treatment group was excluded from the analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences at the same time interval from controls as determined by Dunnett's method for adjusted contrasts. *, $p \leq 0.001$.

TABLE 11
Estimated Post-Mating Ingested Doses (mg/kg of body weight/day) of Oxybenzone in Female and Male Rats[a,b,c]

Post-Mating Dosing Period	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
FEMALE					
GD 0-GD 6	0.0 ± 0.0	282.9 ± 12.4 [207.8 – 443.9]	957.4 ± 33.0 [629.5 – 1,320.5]	5,278.3 ± 181.8 [2,414.2 – 9,231.1]	0.010 ± 0.000 [0.005 – 0.016]
MALE					
GD 0-GD 6	0.0 ± 0.0	202.3 ± 2.1 [164.8 – 261.6]	638.8 ± 8.5 [531.7 – 953.9]	2,213.0 ± 33.7 [1,801.6 – 3,441.1]	0.004 ± 0.000 [0.002 – 0.006]

[a]The mean ingested dose for the post-mating period was calculated by multiplying the dietary concentration of oxybenzone or EE2 by the mean measured amount of food ingested from GD 0 through GD 6 and dividing the result by the mean body weight for the corresponding gestational day. The means for each gestational day were then averaged to determine an approximate mean ingested dose.
[b]Mean dose (mg/kg body weight per day) ± S.E.M.
[c]Numbers in brackets indicate the range of estimated ingested doses; ranges shown are averages of GD 0 through GD 6 data from individual animals.

TABLE 12
Daily Post-Mating Food Consumption (g/animal/day) of Male Rats Administered Dietary Oxybenzone[a,b,c]

Food Consumption (Days)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
GD 0-6	26.3 ± 1.5 (13)	26.5 ± 1.3 (18)	25.2 ± 1.3 (19)	26.9 ± 1.4 (16)	26.8 ± 1.2 (20)

[a]Mean daily food consumption (g/animal/day) ± S.E.M. Numbers in parentheses indicate number of animals per treatment group. Food consumption data was missing for one male in the OXY 3,000 ppm and OXY 30,000 ppm treatment groups.
[b]Males were fed dosed chow for at least 10 weeks prior to mating. Dosing was continuous through GD 6 of the female's pregnancy.
[c]ANOVA results: Treatment, p = 0.880.
Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant pairwise differences were observed between control and treatment groups.

TABLE 13
Absolute Organ Weights (g) of Female Rats Administered Dietary Oxybenzone[a,b]

Organ Weight (g)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Adrenal Glands[c]	0.059 ± 0.002 (11)	0.064 ± 0.001* (18)	0.060 ± 0.001 (18)	0.060 ± 0.001 (17)	0.057 ± 0.001 (19)
Liver[d]**	11.52 ± 0.229 (12)	11.14 ± 0.175 (18)	11.78 ± 0.170 (18)	12.17 ± 0.181 (17)	12.05 ± 0.183 (19)
Kidney, Paired[e]	1.705 ± 0.025 (12)	1.710 ± 0.019 (18)	1.738 ± 0.019 (18)	1.698 ± 0.020 (17)	1.696 ± 0.020 (19)
Ovary, Paired[f]	0.111 ± 0.004 (12)	0.121 ± 0.003 (18)	0.124 ± 0.003* (18)	0.109 ± 0.003 (17)	0.098 ± 0.003* (19)
Thyroid Gland[g]	0.023 ± 0.002 (12)	0.026 ± 0.001 (18)	0.024 ± 0.001 (18)	0.022 ± 0.001 (17)	0.023 ± 0.001 (19)

[a]Mean organ weight (g) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of pregnant females per treatment group.
[b]Paired values represent actual means of the summed values for each animal.
[c]ANOCOVA results: Weight at Sacrifice, p = 0.726; Treatment, p = 0.003.
[d]ANOCOVA results: Weight at Sacrifice, p = <0.001; Treatment, p = 0.003.
[e]ANOCOVA results: Weight at Sacrifice, p = 0.006; Treatment, p = 0.564.
[f]ANOCOVA results: Weight at Sacrifice, p = 0.005; Treatment, p = <0.001.
[g]ANOCOVA results: Weight at Sacrifice, p = 0.935; Treatment, p = 0.343.
Asterisks (*) adjacent to organ weight designation in shaded cells indicate significant linear trends in least square mean comparisons of pregnant female organ weights; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p \leq 0.05$; **, $p < 0.01$.

TABLE 14
Absolute Organ Weights (g) of Male Rats Administered Dietary Oxybenzone[a,b]

Organ Weight (g)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Adrenal Glands[c]	0.053 ± 0.001 (22)	0.052 ± 0.001 (25)	0.052 ± 0.001 (20)	0.055 ± 0.001 (20)	0.053 ± 0.001 (24)
Epididymis, Paired[d]	1.316 ± 0.019 (22)	1.302 ± 0.017 (25)	1.300 ± 0.019 (20)	1.325 ± 0.019 (21)	1.368 ± 0.019 (24)
Liver[e]* **	13.63 ± 0.248 (22)	13.61 ± 0.223 (25)	14.74 ± 0.251** (20)	16.14 ± 0.248 *** (21)	14.65 ± 0.243* (24)
Kidney, Paired[f]* **	2.415 ± 0.043 (22)	2.493 ± 0.039 (25)	2.653 ± 0.044*** (20)	2.772 ± 0.045*** (20)	2.518 ± 0.043 (24)
LABC[g]	1.132 ± 0.024 (22)	1.181 ± 0.022 (25)	1.208 ± 0.025 (20)	1.130 ± 0.024 (21)	1.151 ± 0.024 (24)
Preputial Glands[h]	0.149 ± 0.014 (22)	0.164 ± 0.013 (25)	0.142 ± 0.014 (20)	0.165 ± 0.014 (21)	0.182 ± 0.014 (24)
Dorsolateral Prostate[i]	0.475 ± 0.019 (22)	0.460 ± 0.017 (25)	0.451 ± 0.019 (20)	0.429 ± 0.019 (21)	0.456 ± 0.019 (24)
Ventral Prostate[j]*	0.698 ± 0.028 (22)	0.653 ± 0.025 (25)	0.662 ± 0.028 (20)	0.601 ± 0.028 (21)	0.646 ± 0.027 (24)
Seminal Vesicles with Coagulating Glands[k]	1.259 ± 0.046 (22)	1.259 ± 0.041 (25)	1.415 ± 0.046* (20)	1.297 ± 0.046 (21)	1.355 ± 0.045 (24)
Testis, Paired[l]*	3.796 ± 0.052 (22)	3.748 ± 0.046 (25)	3.755 ± 0.052 (20)	3.919 ± 0.052 (21)	3.983 ± 0.051 (24)
Thyroid Gland[m]	0.025 ± 0.001 (22)	0.025 ± 0.001 (25)	0.025 ± 0.001 (20)	0.025 ± 0.001 (21)	0.025 ± 0.001 (24)
Cowper's Glands, Paired[n]	0.094 ± 0.003 (22)	0.095 ± 0.002 (25)	0.092 ± 0.003 (20)	0.093 ± 0.003 (20)	0.091 ± 0.003 (24)

Abbreviations: LABC = levator ani bulbocavernosus muscle group

[a]Mean organ weight (g) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of males per treatment group.
[b]Paired values represent actual means of the summed values for each animal.
[c]ANOCOVA results: Weight at Sacrifice, p = 0.077; Treatment, p = 0.659.
[d]ANOCOVA results: Weight at Sacrifice, p = 0.001; Treatment, p = 0.107.
[e]ANOCOVA results: Weight at Sacrifice, p = <0.001; Treatment, p = <0.001.
[f]ANOCOVA results: Weight at Sacrifice, p = <0.001; Treatment, p = <0.001.
[g]ANOCOVA results: Weight at Sacrifice, p = 0.001; Treatment, p = 0.101.
[h]ANOCOVA results: Weight at Sacrifice, p = 0.400; Treatment, p = 0.380.
[i]ANOCOVA results: Weight at Sacrifice, p = 0.103; Treatment, p = 0.568.
[j]ANOCOVA results: Weight at Sacrifice, p = 0.214; Treatment, p = 0.238.
[k]ANOCOVA results: Weight at Sacrifice, p = 0.024; Treatment, p = 0.060.
[l]ANOCOVA results: Weight at Sacrifice, p = <0.001; Treatment, p = 0.008.
[m]ANOCOVA results: Weight at Sacrifice, p = 0.015; Treatment, p = 0.980.
[n]ANOCOVA results: Weight at Sacrifice, p = 0.027; Treatment, p = 0.798.
Asterisks (*) adjacent to organ weight designation in shaded cells indicate significant linear trends in least square mean comparisons of male organ weights; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to means in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$; ***, $p \leq 0.001$.

TABLE 15
Summary Statistics of Organ Weight (mg) to Body Weight (g) Ratios of Female Rats Administered Dietary Oxybenzone[a,b]

Organ Weight (mg)/Body Weight (g)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Liver	37.16 ± 0.87 (12)	35.75 ± 0.52 (18)	37.63 ± 0.61 (18)	38.64 ± 0.43 (17)	38.14 ± 0.41 (19)
Kidney, Paired	5.329 ± 0.080 (12)	5.407 ± 0.067 (18)	5.518 ± 0.059 (18)	5.474 ± 0.049 (17)	5.507 ± 0.070 (19)
Thyroid Gland	0.071 ± 0.005 (12)	0.081 ± 0.004 (18)	0.074 ± 0.005 (18)	0.071 ± 0.004 (17)	0.075 ± 0.004 (19)

[a]Summary mean (g) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of pregnant females per treatment group.
[b]Relative organ weight to body weight ratios are not included for the adrenal gland or ovaries as past studies have indicated these organ weights are not affected by changes in body weight during normal growth (Bailey et al., 2004).

TABLE 16
Summary Statistics of Organ Weight (mg) to Body Weight (g) Ratios of Male Rats Administered Dietary Oxybenzone[a,b]

Organ Weight (mg)/ Body Weight (g)	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Liver	34.84 ± 0.48 (22)	34.54 ± 0.56 (25)	37.46 ± 0.76 (20)	40.56 ± 0.72 (21)	36.48 ± 0.45 (24)
Kidney, Paired	6.097 ± 0.089 (22)	6.295 ± 0.077 (25)	6.675 ± 0.108 (20)	7.020 ± 0.145 (20)	6.368 ± 0.095 (24)
LABC	2.805 ± 0.056 (22)	2.959 ± 0.050 (25)	3.104 ± 0.059 (20)	2.906 ± 0.077 (21)	2.985 ± 0.061 (24)
Preputial Glands	0.371 ± 0.023 (22)	0.410 ± 0.044 (25)	0.357 ± 0.025 (20)	0.426± 0.029 (21)	0.471 ± 0.031 (24)
Dorsolateral Prostate	1.181 ± 0.055 (22)	1.150 ± 0.043 (25)	1.126 ± 0.044 (20)	1.099 ± 0.030 (21)	1.182 ± 0.052 (24)
Ventral Prostate	1.722 ± 0.062 (22)	1.636 ± 0.067 (25)	1.643 ± 0.067 (20)	1.546 ± 0.062 (21)	1.690 ± 0.072 (24)
Seminal Vesicles, Paired[c]	3.135 ± 0.094 (22)	3.163 ± 0.108 (25)	3.530 ± 0.120 (20)	3.326 ± 0.108 (21)	3.502 ± 0.114 (24)
Thyroid Gland	0.062 ± 0.002 (22)	0.063 ± 0.003 (25)	0.062 ± 0.003 (20)	0.065 ± 0.002 (21)	0.064 ± 0.003 (24)
Cowper's Glands, Paired	0.233 ± 0.006 (22)	0.237 ± 0.007 (25)	0.229 ± 0.006 (20)	0.239 ± 0.007 (20)	0.235 ± 0.006 (24)

Abbreviations: LABC = levator ani bulbocavernosus muscle group

[a]Summary mean (g) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of males per treatment group.
[b]Relative organ weight to body weight ratios are not included for the testis, epididymis or adrenal glands as past studies have indicated these organ weights are not affected by changes in body weight during normal growth (Bailey et al., 2004).
[c]Seminal vesicle weights also include the weight of the coagulating glands.

TABLE 17
Estrus Cycle Stage Proportion Analysis of Female Rats Administered Dietary Oxybenzone[a]

Stage (%)[b]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Proestrus	6.0	4.6	9.0	4.3	8.7
Estrus	25.4	23.0	25.8	22.7	20.2
Diestrus	65.7	69.6	63.9	70.2	68.9

[a]Vaginal swabs were collected daily for 14 days from the initiation of dosing. Daily swabs were reported as proestrus, estrus or diestrus. Swabs were collected from 25 animals in each treatment group.
[b]Least squares mean stage percentages across treatments. Analysis was performed using arcsine-squareroot transformed data.
Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant pairwise differences were observed between control and treatment groups.

TABLE 18
Estrus Cycle Abnormalities in Female Rats Administered Dietary Oxybenzone[a]

Pattern[b]	Estrus Cycle	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
		CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Excessive Proestrus	*Significance*[c]	-	-	-	-	-
	Normal	96.0% (24)	92.0% (23)	100.0% (25)	100.0% (25)	96.0% (24)
	Abnormal	4.0% (1)	8.0% (2)	0.0% (0)	0.0% (0)	4.0% (1)
Extended Estrus	*Significance*[c]	-	-	-	-	-
	Normal	80.0% (20)	88.0% (22)	88.0% (22)	92.0% (23)	92.0% (23)
	Abnormal	20.0% (5)	12.0% (3)	12.0% (3)	8.0% (2)	8.0% (2)
Extended Diestrus	*Significance*[c]	-	-	-	-	*
	Normal	76.0% (19)	56.0% (14)	64.0% (16)	56.0% (14)	44.0% (11)
	Abnormal	24.0% (6)	44.0% (11)	36.0% (9)	44.0% (11)	56.0% (14)
Any Abnormal Cycling	*Significance*[c]	-	-	-	-	-
	Normal	52.0% (13)	40.0% (10)	56.0% (14)	48.0% (12)	36.0% (9)
	Abnormal	48.0% (12)	60.0% (15)	44.0% (11)	52.0% (13)	64.0% (16)

[a]Values presented are the percentages of animals with either normal patterns for all cycles occurring over the time period assessed or one or more abnormal cycles of the pattern listed in the first column of the table. Numbers in parentheses indicate number of females with normal or abnormal cycles per treatment group.
[b]Endpoints evaluated were any abnormal cycling, excessive proestrus, extended estrus and extended diestrus. Extended estrus was defined as more than two consecutive days of estrus; extended diestrus was defined as more than four consecutive days of diestrus; excessive proestrus was defined as two or more consecutive days of proestrus in a cycle.
[c]Abnormal cycling was defined by the 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 was used for comparisons of dosed groups to control. The Cochran-Armitage test was used for analysis of trend. The result reported in the CTRL column is the trend test. "-" = no significance; * $p < 0.05$.

TABLE 19
Estrus Cycle Stage Transition Counts and Proportions in Female Rats Administered Dietary Oxybenzone[a,b,c]

Treatment	From	To N	To EX	To DX	Total	N%	EX%	DX%	P Value
CTRL	N	251	5	6	262	95.8	1.9	2.3	-
	EX	4	2	-	6	66.7	33.3	-	
	DX	3	-	36	39	7.7	-	92.3	
OXY 3,000	N	257	3	11	271	94.8	1.1	4.1	0.443
	EX	3	0	-	3	100.0	0.0	-	
	DX	5	-	34	39	12.8	-	87.2	
OXY 10,000	N	284	3	9	296	95.9	1.0	3.0	0.537
	EX	3	0	-	3	100.0	0.0	-	
	DX	3	-	17	20	15.0	-	85.0	
OXY 30,000	N	263	2	12	277	94.9	0.7	4.3	0.117
	EX	2	0	-	2	100.0	0.0	-	
	DX	8	-	27	35	22.9	-	77.1	
EE2 0.05	N	260	2	16	278	93.5	0.7	5.8	0.098
	EX	2	0	-	2	100.0	0.0	-	
	DX	6	-	30	36	16.7	-	83.3	

Abbreviations: N = normal transition, EX = extended estrus, DX = extended diestrus

[a]For analysis, the first day of estrus with transition to a second day of estrus was considered normal. Subsequent transitions to estrus were defined as extended. Four consecutive days of diestrus was considered normal, subsequent transitions to diestrus were defined as extended. Abnormal cycling transitions were not defined for proestrus. The analysis only considered the transition to the first proestrus as normal; subsequent transitions were treated as missing.
[b]From EX to DX and from DX to EX are not possible transitions.
[c]Transition matrices of treatment groups were compared to the control group for analyses based on the Markov chain model of Girard and Sager (1987). Shown are the counts and proportions observed; expected transition counts and percentages are provided in Appendix XIX. Analysis was performed using Markov chains with the chi square statistic to test for differences between treated groups and control. No adjustment for multiple comparisons was performed. Abnormality was determined by differences in the observed and expected transitions. No statistical significant differences were observed between control and treatment groups.

TABLE 20
Estrus Cycle Length (days) of Female Rats Administered Dietary Oxybenzone[a]

Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Cycle Length (days)[b]	4.83 ± 0.23 (20)	4.57 ± 0.23 (20)	4.81 ± 0.21 (24)	5.22 ± 0.25 (21)	5.04 ± 0.24 (19)

[a]Mean cycle length (days) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of animals in the analysis which includes those with at least one uncensored cycle.
[b]For analysis of estrus cycle length, cycle days were defined from the first day of estrus in a sequence of stages until the first day of estrus in the following sequence. Cycles were considered censored if the last stage was either diestrus or proestrus. Analysis was performed using non-censored cycles.
Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant pairwise differences were observed between control and treatment groups.

TABLE 21
Reproductive Parameters of Female Rats Administered Dietary Oxybenzone

Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Number Mated[a]	20 (80.0%)	22 (88.0%)	25 (100.0%)	22 (88.0%)	22 (88.0%)
Time to Mating in Days[b]	4.5 (3.0-8.0)	4.0 (2.0-6.0)	5.0 (4.0-7.0)	5.0 (3.0-6.0)	6.0 (4.0-9.0)

[a]N is equal to 25 for all treatment groups. Numbers in parentheses indicate percentage of females mated per treatment group. Proportions of mated females were analyzed using Fisher's Exact test for comparisons of treated groups and using the Cochran-Armitage test for trend; no significant differences were observed.
[b]Values shown represent median time to mating determined by the product-limit analysis method; numbers in parentheses represent 95% confidence limits. Females were considered censored at 14 days if there was no evidence of mating. A Cox proportional hazards model was used for the trend test and comparisons to control; no significant differences were observed. Analysis excluded one female in the CTRL and OXY 30,000 ppm groups due to unknown/undetermined mating dates.

TABLE 22
Pregnancy Parameters of Female Rats Administered Dietary Oxybenzone

Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Number Pregnant[a]	16 (64.0%)	19 (76.0%)	24* (96.0%)	21 (84.0%)	21 (84.0%)
Gravid Uterine Weights (g)[b,c,f]	18.7 ± 1.0 (12)	16.8 ± 0.8 (18)	17.8 ± 0.8 (18)	16.7 ± 0.8 (17)	15.3 ± 0.8* (19)
Number of Implants[d,f]	14.5 ± 1.0 (16)	12.4 ± 0.9 (19)	13.5 ± 0.8 (22)	14.0 ± 0.9 (20)	13.0 ± 0.9 (21)
Number of Resorptions[e,f]	0.6 ± 0.2 (12)	0.6 ± 0.2 (18)	0.4 ± 0.2 (18)	0.5 ± 0.2 (17)	0.7 ± 0.2 (19)

[a]N is equal to 25 for all treatment groups. Numbers in parentheses indicate percentage of pregnant females. Fisher's Exact test was used for comparison of treatments to control; the Cochran-Armitage test was used for analysis of trend across treatments. P-values were adjusted for multiple comparisons using Holm's method. Asterisks adjacent to number pregnant in shaded cells indicate significant differences from controls. *, p = <0.05.
[b]Mean gravid uterine weight (g) ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of animals included in the analysis; exclusions include those with unknown/undetermined mating dates or those dosed past the protocol specified stop date.
[c]Results of a one-way ANOVA: Treatment, p = 0.080.
[d]Counts of implantation sites were analyzed using Poisson regression with terms for treatment and covariate number of corpora lutea. Shown are the mean ± S.E.M. reported by treatment group. There was no significant treatment effect; the covariate corpora lutea was significant (p = 0.008). Excluded from analysis were three dams that littered.
[e]All resorptions were classified as early. Counts of resorptions were analyzed using Poisson regression with terms for treatment and covariate number of implantation sites. Shown are the mean ± S.E.M. reported by treatment group. There was no significant treatment or covariate effect. Excluded from analysis were females with unknown/undetermined mating dates or those dosed past the protocol specified stop date.
[f]Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Asterisks (*) adjacent to means in shaded cells indicate a significant pairwise differences from controls. *, p = <0.05.

TABLE 23
Summary Statistics of Pregnancy Parameters for Female Rats Administered Dietary Oxybenzone[a]

Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Corpora Lutea	16.7 ± 0.4 (16)	17.3 ± 0.6 (19)	16.7 ± 0.5 (24)	14.1 ± 0.4 (21)	13.2 ± 0.3 (21)
Live	14.3 ± 0.5 (12)	12.7 ± 1.0 (18)	13.8 ± 0.4 (18)	12.7 ± 0.4 (17)	11.2 ± 0.5 (19)
Pre-Implantation Loss (%)[b]	8.5 ± 2.5 (16)	23.2 ± 5.1 (19)	13.9 ± 2.5 (22)	5.6 ± 1.5 (20)	9.9 ± 2.7 (21)
Post-Implantation Loss (%)[c]	3.9 ± 1.6 (12)	4.4 ± 1.7 (18)	3.2 ± 1.2 (18)	3.8 ± 1.3 (17)	6.0 ± 1.6 (19)

[a]Summary mean ± S.E.M. reported by treatment group. Numbers in parentheses indicate number of pregnant females per treatment group. Females with an unknown/undetermined mating date or those dosed past the protocol specified stop date were excluded from the analysis of live fetuses and post-implantation loss.
[b]Pre-implantation loss was defined as the percentage of corpora lutea that did not result in implantation.
[c]Post-implantation loss was defined as the percentage of implantations that were resorbed.

TABLE 24
Sperm Motility of Male Rats Administered Dietary Oxybenzone[a,b]

Sperm Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Percent Sperm Motility	70.3 ± 5.8 (9)	74.6 ± 5.5 (10)	67.1 ± 6.1 (8)	79.0 ± 6.5 (7)	77.2 ± 5.5 (10)

[a]Mean percent (%) motile ± S.E.M. Numbers in parentheses indicate number of males per treatment group.
[b]Motility data analyzed using an ANOVA model with Kenward-Roger estimated degrees of freedom. Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant trends or pairwise differences between control and treatment groups were observed.

TABLE 25
Cauda Epididymal Sperm Counts of Male Rats Administered Dietary Oxybenzone[a,b]

Sperm Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Cauda Sperm Counts	1089.4 ± 72.2 (9)	1058.2 ± 68.5 (10)	1105.0 ± 76.6 (8)	1071.1 ± 81.9 (7)	1048.9 ± 68.5 (10)

[a]Mean count (10^6/g of tissue) ± S.E.M. Numbers in parentheses indicate number of males per treatment group.
[b]Data analyzed using an ANOVA model with Kenward-Roger estimated degrees of freedom. Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant trends or pairwise differences between control and treatment groups were observed.

TABLE 26
Testicular Spermatid Head Counts of Male Rats Administered Dietary Oxybenzone[a,b]

Sperm Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Testicular Spermatid Head Counts	127.6 ± 5.9 (9)	125.0 ± 5.6 (10)	120.0 ± 6.3 (8)	127.8 ± 6.7 (7)	123.6 ± 5.6 (10)

[a]Mean count (10^6/g of tissue) ± S.E.M. Numbers in parentheses indicate number of males per treatment group.
[b]Data analyzed using an ANOVA model with Kenward-Roger estimated degrees of freedom. Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant trends or pairwise differences between control and treatment groups were observed.

TABLE 27
Sperm Morphology of Male Rats Administered Dietary Oxybenzone[a,b,c,d]

Sperm Parameter	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL	OXY 3,000	OXY 10,000	OXY 30,000	EE2 0.05
Abnormal Morphology	0.22 ± 0.15 (9)	0.50 ± 0.21 (10)	1.0 ± 0.33 (8)	0.43 ± 0.23 (7)	0.10 ± 0.09 (10)

[a]Mean abnormal counts per animal ± S.E.M.. Numbers in parentheses indicate number of males per treatment group.
[b]A minimum of 200 caudal epididymal sperm per animal were microscopically evaluated for head (amorphous, small, enlarged) or tail (coiled, bent, double) abnormalities and the mean number of sperm containing abnormalities was calculated.
[c]No sperm head abnormalities were observed in any treatment group.
[d]Data analyzed using a generalized linear model with a Poisson distribution and a log link function. Each treatment was compared to the control group and adjustment for multiple comparisons was performed using Hochberg's method. No significant trends or pairwise differences between control and treatment groups were observed.

TABLE 28
Hematological Parameters of Females Rats Administered Dietary Oxybenzone[a]

Hematological Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n =8	**OXY 3,000** n = 10	**OXY 10,000** n = 10	**OXY 30,000** n = 10	**EE2 0.05** n = 10
WBC (10^3/mm^3) [p = 0.286]	8.1 ± 0.5 [8.2] (5.8 – 10.5)	9.2 ± 0.6 [9.7] (6.1 – 11.3)	8.2 ± 0.6 [8.2] (4.4 – 11.0)	8.6 ± 0.6 [8.9] (5.3 – 11.5)	7.0 ± 0.8 [7.4] (2.9 – 11.0)
NEU (%)** *[p = 0.025]*	28.7 ± 2.0 [27.3] (20.6 – 36.1)	23.4 ± 2.2 [22.1] (16.2 – 40.3)	23.8 ± 1.3 [21.8] (20.5 – 32.0)	20.8 ± 1.2** [19.6] (17.1 - 28.5)	25.5 ± 2.2 [25.5] (13.6 – 36.2)
LYM (%) [p = 0.287]	63.2 ± 2.6 [62.1] (53.8 – 74.4)	66.4 ± 2.6 [67.8] (52.5 – 74.4)	67.4 ± 2.4 [69.0] (54.0 – 74.4)	70.1 ± 1.7 [69.3] (62.9 – 76.6)	65.3 ± 2.5 [62.6] (55.3 – 81.5)
MON (%) [p = 0.907]	7.2 ± 1.2 [5.7] (4.0 – 14.6)	8.9 ± 1.4 [8.0] (4.6 – 19.5)	8.0 ± 1.4 [7.6] (2.7 – 15.7)	7.8 ± 0.9 [7.2] (4.6 – 12.1)	8.2 ± 1.3 [6.7] (4.8 – 16.8)
EOS (%) *[p = 0.027]*	0.9 ± 0.1 [1.0] (0.6 – 1.1)	1.1 ± 0.1 [1.2] (0.6 – 1.7)	0.8 ± 0.1 [0.7] (0.5 – 1.1)	1.1 ± 0.0 [1.1] (0.9 – 1.2)	0.9 ± 0.1 [0.9] (0.1 – 1.5)
BAS (%) [p = 0.507]	0.11 ± 0.02 [0.10] (0.00 – 0.20)	0.19 ± 0.06 [0.10] (0.10 – 0.70)	0.11 ± 0.02 [0.10] (0.00 – 0.30)	0.13 ± 0.02 [0.10] (0.10 – 0.20)	0.11 ± 0.03 [0.10] (0.00 – 0.30)
NEU (10^3/mm^3) [p = 0.404]	2.35 ± 0.26 [2.35] (1.19 – 3.56)	2.13 ± 0.19 [2.16] (1.35 – 3.29)	1.93 ± 0.14 [1.90] (1.19 – 2.53)	1.79 ± 0.15 [1.67] (1.23 – 2.60)	1.88 ± 0.30 [1.88] (0.39 – 3.71)
LYM (10^3/mm^3) *[p = 0.044]*	5.08 ± 0.33 [4.85] (4.05 – 6.45)	6.15 ± 0.48 [6.45] (4.05 – 8.39)	5.59 ± 0.48 [5.63] (2.91 – 8.09)	6.03 ± 0.35 [6.25] (3.45 – 7.62)	4.47 ± 0.44 [4.55] (2.34 – 6.46)
MON (10^3/mm^3) [p = 0.685]	0.59 ± 0.11 [0.53] (0.23 – 1.21)	0.83 ± 0.15 [0.69] (0.39 – 1.91)	0.66 ± 0.12 [0.61] (0.20 – 1.26)	0.72 ± 0.12 [0.64] (0.30 – 1.27)	0.61 ± 0.14 [0.48] (0.14 – 1.50)
EOS (10^3/mm^3) *[p = 0.023]*	0.07 ± 0.01 [0.07] (0.05 – 0.12)	0.11 ± 0.01 [0.10] (0.05 – 0.19)	0.06 ± 0.01 [0.06] (0.04 – 0.10)	0.09 ± 0.01 [0.09] (0.06 – 0.14)	0.07 ± 0.01 [0.07] (0.00 – 0.11)
BAS (10^3/mm^3) [p = 0.279]	0.01 ± 0.00 [0.01] (0.00 – 0.02)	0.02 ± 0.01 [0.01] (0.01 – 0.08)	0.01 ± 0.00 [0.01] (0.00 – 0.02)	0.01 ± 0.00 [0.01] (0.01 – 0.02)	0.01 ± 0.00 [0.01] (0.00 – 0.02)
RBC (10^6/mm^3) *[p = 0.027]*	6.73 ± 0.09 [6.68] (6.31 – 7.22)	6.86 ± 0.11 [6.90] (6.47 – 7.34)	6.63 ± 0.08 [6.68] (6.19 – 6.92)	6.71 ± 0.09 [6.71] (6.29 – 7.30)	7.05 ± 0.07* [7.11] (6.69 – 7.31)

TABLE 28
Hematological Parameters of Female Rats Administered Dietary Oxybenzone Continued[a]

Hematological Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n =8	OXY 3,000 n = 10	OXY 10,000 n = 10	OXY 30,000 n = 10	EE2 0.05 n = 10
HGB (g/dL) *[p = 0.029]*	13.3 ± 0.2 [13.1] (12.6 – 14.2)	13.6 ± 0.2 [13.5] (12.9 – 15.0)	13.3 ± 0.1 [13.3] (12.7 – 13.7)	13.4 ± 0.2 [13.4] (12.6 – 14.7)	14.0 ± 0.1** [14.0] (13.5 – 14.7)
HCT (%) [p = 0.071]	38.3 ± 0.8 [37.8] (35.8 – 41.9)	38.9 ± 0.6 [39.0] (35.5 – 42.7)	37.9 ± 0.4 [38.2] (35.8 – 39.5)	38.4 ± 0.6 [38.3] (36.1 – 41.9)	40.1 ± 0.5 [40.2] (37.7 – 43.0)
MCV (μm^3) [p = 0.969]	57.0 ± 0.5 [57.0] (55.0 – 59.0)	56.6 ± 0.6 [56.5] (53.0 – 59.0)	57.2 ± 0.4 [57.5] (55.0 – 59.0)	57.0 ± 0.6 [57.0] (55.0 – 61.0)	56.9 ± 0.5 [57.0] (55.0 – 59.0)
MCH (pg) [p = 0.576]	19.7 ± 0.1 [19.7] (19.2 – 20.3)	19.9 ± 0.2 [20.0] (18.3 – 21.0)	20.0 ± 0.2 [20.0] (19.1 – 20.9)	20.0 ± 0.2 [20.0] (18.7 – 21.4)	19.8 ± 0.2 [19.9] (19.0 – 20.7)
MCHC (g/dL) [p = 0.892]	34.6 ± 0.3 [34.9] (33.3 – 35.8)	35.1 ± 0.2 [35.0] (34.5 – 36.2)	35.0 ± 0.2 [35.3] (33.2 – 35.6)	35.0 ± 0.1 [35.0] (34.0 – 35.6)	34.9 ± 0.2 [35.2] (33.5 – 35.9)
PLT ($10^3/mm^3$) [p = 0.578]	751.0 ± 21.7 [748.0] (675.0 – 859.0)	735.1 ± 38.9 [738.5] (557.0 – 901.0)	793.2 ± 27.7 [788.0] (678.0 – 911.0)	794.4 ± 36.9 [815.0] (601.0 – 953.0)	795.3 ± 16.8 [797.5] (702.0 – 873.0)
PCV (%) [p = 0.083]	38.5 ± 0.7 [38.0] (36.0 – 42.0)	38.9 ± 0.6 [39.0] (35.5 – 42.5)	38.0 ± 0.4 [38.0] (35.5 – 40.0)	38.7 ± 0.6 [38.3] (36.0 – 42.0)	40.2 ± 0.4 [40.3] (38.0 – 43.0)
Reticulocyte (%) [p = 0.877]	3.5 ± 0.1 [3.3] (3.1 – 3.9)	3.3 ± 0.1 [3.5] (2.8 – 3.8)	3.3 ± 0.1 [3.4] (2.8 – 3.9)	3.4 ± 0.1 [3.4] (2.9 – 3.9)	3.3 ± 0.1 [3.2] (2.8 – 3.7)

Abbreviations: WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils; RBC = red blood cells; HGB = hemoglobin concentration; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; PLT = platelets; PCV = packed cell volume

[a]Parametric summary means ± S.E.M. Nonparametric median values are reported in brackets. Numbers in parentheses indicate minimum and maximum nonparametric summary statistic values.
[b]Two pregnant females were excluded from the analysis of the CTRL animals; one female had an unknown mating date while the other was dosed past the protocol specified end date (GD 6).
[c]ANOVA results are presented in brackets for each hematological parameter analyzed. ANOVA was performed using a nonparametric method with midranks (using the average of left and right ranks for ties) and an unstructured covariance (Brunner et al., 2002). Analysis that indicated significant treatment effects are shown in italics; significance level was set at $p = 0.05$.
Asterisks (*) adjacent to hematological endpoints in shaded cells indicate significant trends in least square mean comparisons of oxybenzone and controls; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to mean values in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$.

TABLE 29
Hematological Parameters of Male Rats Administered Dietary Oxybenzone[a]

Hematological Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 9	OXY 3,000 n = 10	OXY 10,000[b] n = 8	OXY 30,000[b] n = 7	EE2 0.05 n = 10
WBC (10^3/mm^3) [p = 0.394]	6.6 ± 0.5 [6.2] (3.6 – 9.3)	6.1 ± 0.8 [5.6] (3.3 – 10.2)	8.0 ± 0.8 [7.8] (4.0 – 11.4)	6.8 ± 1.0 [5.7] (4.3 – 11.9)	6.8 ± 0.4 [6.3] (5.3 – 9.0)
NEU (%) [p = 0.749]	14.6 ± 1.5 [12.7] (10.6 – 23.9)	14.0 ± 1.6 [12.7] (9.1 – 22.4)	14.4 ± 1.6 [14.4] (9.0 – 22.5)	12.1 ± 1.1 [11.6] (8.3 – 15.5)	15.6 ± 1.9 [15.7] (8.8 – 30.1)
LYM (%) [p = 0.394]	79.9 ± 1.8 [80.9] (70.0 – 86.2)	80.7 ± 1.8 [82.6] (72.1 – 86.7)	79.4 ± 1.6 [79.2] (71.8 – 86.3)	83.4 ± 1.3 [82.3] (78.6 – 88.1)	79.3 ± 2.0 [80.5] (65.2 – 86.7)
MON (%) [p = 0.596]	4.3 ± 0.4 [3.8] (3.0 – 7.2)	4.4 ± 0.4 [4.2] (2.9 – 6.4)	4.8 ± 0.7 [4.9] (2.1 – 8.0)	3.5 ± 0.7 [2.5] (1.8 – 6.4)	4.1 ± 0.3 [3.9] (2.7 – 5.6)
EOS (%) [p = 0.187]	1.1 ± 0.2 [1.1] (0.1 – 1.7)	0.8 ± 0.2 [1.0] (0.0 – 1.5)	1.2 ± 0.1 [1.4] (0.4 – 1.6)	0.8 ± 0.2 [0.7] (0.2 – 1.7)	0.9 ± 0.1 [0.9] (0.2 – 1.5)
BAS (%) [p = 0.259]	0.10 ± 0.00 [0.10] (0.10 – 0.10)	0.07 ± 0.02 [0.10] (0.00 – 0.10)	0.11 ± 0.02 [0.10] (0.00 – 0.20)	0.13 ± 0.03 [0.10] (0.00 – 0.20)	0.10 ± 0.00 [0.10] (0.10 – 0.10)
NEU (10^3/mm^3) [p = 0.342]	0.97 ± 0.12 [0.91] (0.38 – 1.52)	0.86 ± 0.16 [0.83] (0.34 – 2.09)	1.13 ± 0.15 [1.01] (0.71 – 1.74)	0.84 ± 0.18 [0.73] (0.48 – 1.85)	1.07 ± 0.19 [0.94] (0.56 – 2.69)
LYM (10^3/mm^3) [p = 0.517]	5.28 ± 0.46 [5.01] (3.13 – 7.89)	4.92 ± 0.68 [4.49] (2.55 – 8.64)	6.38 ± 0.67 [6.34] (3.15 – 9.06)	5.64 ± 0.79 [4.68] (3.76 – 9.38)	5.39 ± 0.33 [5.16] (4.14 – 7.62)
MON (10^3/mm^3) [p = 0.566]	0.29 ± 0.04 [0.28] (0.11 – 0.52)	0.27 ± 0.04 [0.24] (0.10 – 0.45)	0.41 ± 0.08 [0.40] (0.08 – 0.87)	0.27 ± 0.07 [0.14] (0.08 – 0.55)	0.28 ± 0.03 [0.31] (0.16 – 0.36)
EOS (10^3/mm^3) [p = 0.053]	0.07 ± 0.01 [0.08] (0.00 – 0.10)	0.06 ± 0.02 [0.07] (0.00 – 0.15)	0.11 ± 0.02 [0.11] (0.02 – 0.17)	0.06 ± 0.02 [0.04] (0.01 – 0.13)	0.06 ± 0.01 [0.06] (0.01 – 0.09)
BAS (10^3/mm^3) [p = 0.346]	0.01 ± 0.00 [0.01] (0.00 – 0.01)	0.01 ± 0.00 [0.01] (0.00 – 0.01)	0.01 ± 0.00 [0.01] (0.00 – 0.02)	0.01 ± 0.00 [0.01] (0.00 – 0.02)	0.01 ± 0.00 [0.01] (0.01- 0.01)
RBC (10^6/mm^3)* [p = 0.110]	8.63 ± 0.10 [8.64] (8.10 – 9.00)	8.77 ± 0.08 [8.83] (8.33 – 9.06)	8.84 ± 0.15 [8.83] (8.01 – 9.34)	8.43 ± 0.10 [8.40] (8.09 – 8.90)	8.79 ± 0.16 [8.71] (8.21 – 9.89)

TABLE 29
Hematological Parameters of Male Rats Administered Dietary Oxybenzone Continued[a]

Hematological Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 9	OXY 3,000 n = 10	OXY 10,000[b] n = 8	OXY 30,000[b] n = 7	EE2 0.05 n = 10
HGB (g/dL)** *[p = 0.003]*	16.3 ± 0.1 [16.2] (15.9 – 17.3)	16.0 ± 0.1 [16.1] (15.6 – 16.6)	16.3 ± 0.2 [16.4] (15.4 – 17.0)	15.8 ± 0.2* [15.9] (15.1 – 16.2)	16.8 ± 0.3 [16.8] (15.8 – 18.6)
HCT (%)*** *[p = 0.004]*	48.5 ± 0.5 [49.1] (46.3 – 50.5)	47.3 ± 0.3 [47.3] (45.5 – 48.9)	48.6 ± 0.8 [48.6] (44.4 – 52.3)	46.2 ± 0.4** [46.4] (44.2 – 47.6)	49.4 ± 0.8 [48.7] (45.4 – 53.9)
MCV (μm^3) *[p = 0.048]*	56.2 ± 0.6 [57.0] (52.0 – 58.0)	54.1 ± 0.3** [54.5] (52.0 – 55.0)	55.0 ± 0.6 [55.0] (52.0 – 57.0)	54.9 ± 0.9 [55.0] (52.0 – 58.0)	56.4 ± 0.5 [56.5] (55.0 – 59.0)
MCH (pg) [p = 0.092]	18.9 ± 0.3 [19.3] (17.7 – 19.9)	18.3 ± 0.2 [18.2] (17.5 – 19.1)	18.5 ± 0.2 [18.5] (17.6 – 19.4)	18.7 ± 0.3 [19.0] (17.7 – 19.6)	19.1 ± 0.1 [19.2] (18.6 – 19.7)
MCHC (g/dL) [p = 0.725]	33.6 ± 0.3 [34.2] (32.5 – 34.5)	34.0 ± 0.2 [34.3] (32.3 – 34.9)	33.6 ± 0.3 [33.6] (32.4 – 34.7)	34.1 ± 0.0 [34.1] (34.0 – 34.3)	34.1 ± 0.2 [34.3] (32.8 – 34.8)
PLT ($10^3/mm^3$) [p = 0.347]	673.9 ± 29.6 [661.0] (563.0 – 822.0)	654.0 ± 14.2 [645.0] (578.0 – 742.0)	670.5 ± 16.2 [669.5] (597.0 -724.0)	695.4 ± 24.8 [676.0] (618.0 – 792.0)	638.5 ± 14.5 [617.5] (594.0 -721.0)
PCV (%)*** *[p = 0.004]*	48.7 ± 0.5 [49.0] (46.0 – 50.5)	47.3 ± 0.3 [47.5] (45.5 – 48.5)	48.6 ± 0.9 [48.3] (44.0 – 52.5)	46.4 ± 0.4** [46.5] (44.5 – 47.5)	49.5 ± 0.8 [48.8] (45.5 -54.0)
Reticulocyte (%) [p = 0.660]	1.2 ± 0.1 [1.2] (0.8 – 1.7)	1.3 ± 0.1 [1.4] (0.9 – 1.6)	1.2 ± 0.1 [1.2] (0.8 – 1.6)	1.3 ± 0.1 [1.1] (1.0 – 1.7)	1.3 ± 0.1 [1.4] (0.8 – 1.8)

Abbreviations: WBC = white blood cells; NEU = neutrophils; LYM = lymphocytes; MON = monocytes; EOS = eosinophils; BAS = basophils; RBC = red blood cells; HGB = hemoglobin concentration; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; PLT = platelets; PCV = packed cell volume

[a]Parametric summary means ± S.E.M. Nonparametric median values are reported in brackets. Numbers in parentheses indicate minimum and maximum nonparametric summary statistic values.
[b]A total of six males were excluded from the analysis; all had either unknown/undetermined mating dates.
[c]ANOVA results are presented in brackets for each hematological parameter analyzed. ANOVA was performed using a nonparametric method with midranks (using the average of left and right ranks for ties) and an unstructured covariance (Brunner et al., 2002). Analysis that indicated significant treatment effects are shown in italics; significance level was set at p = 0.05.
Asterisks (*) adjacent to hematological endpoints in shaded cells indicate significant trends in least square mean comparisons of oxybenzone and controls; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to mean values in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$; ***, $p = 0.001$.

TABLE 30
Clinical Chemistry Parameters of Female Rats Administered Dietary Oxybenzone[a]

Clinical Chemistry Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 8	**OXY 3,000** n = 10	**OXY 10,000** n = 10	**OXY 30,000** n = 10	**EE2 0.05** n = 10
SDH (U/L)** *[p = 0.002]*	16.6 ± 3.5 [14.4] (7.3 – 36.6)	5.8 ± 1.3** [6.8] (0.5 – 10.8)	12.9 ± 2.2 [13.2] (2.0 – 24.1)	6.0 ± 1.0** [4.7] (1.9 – 12.2)	9.5± 1.6 [9.8] (1.5 – 19.4)
TBA (µmol/L) [p = 0.373]	62.2 ± 11.4 [48.3] (31.9 – 115.6)	69.9 ± 5.7 [75.8] (41.3 – 91.0)	69.1 ± 7.9 [66.3] (36.7 – 100.9)	68.3 ± 9.6 [63.6] (37.1 – 146.1)	85.3 ± 8.3 [78.5] (51.1 – 118.9)
ALB (g/dL) [p = 0.933]	3.6 ± 0.1 [3.7] (3.4 – 4.0)	3.6 ± 0.1 [3.7] (3.1 – 3.8)	3.7 ± 0.0 [3.7] (3.5 – 3.9)	3.6 ± 0.0 [3.6] (3.4 – 3.8)	3.6 ± 0.1 [3.7] (3.2 – 3.8)
ALT (U/L) [p = 0.152]	78.0 ± 4.7 [76.5] (62.0 – 99.0)	74.2 ± 4.5 [69.5] (54.0 – 95.0)	72.5 ± 3.9 [71.5] (56.0 – 92.0)	85.1 ± 5.1 [83.5] (64.0 – 120.0)	85.8 ± 3.6 [89.0] (64.0 – 98.0)
ALP (U/L) [p = 0.690]	179.4 ± 13.4 [185.5] (123.0 – 231.0)	160.7 ± 7.9 [168.5] (109.0 – 187.0)	171.2 ± 3.9 [166.5] (157.0 – 198.0)	176.8 ± 6.3 [179.0] (144.0 – 210.0)	167.1 ± 10.5 [176.5] (103.0 – 211.0)
AST (U/L)* [p = 0.222]	106.8 ± 8.7 [101.0] (84.0 – 149.0)	105.9 ± 14.1 [89.0] (69.0 – 192.0)	107.7 ± 14.4 [97.5] (72.0 – 226.0)	87.7 ± 6.5* [81.5] (68.0 – 142.0)	103.6 ± 17.7 [86.0] (76.0 – 261.0)
TRIG (mg/dL) [p = 0.848]	162.0 ± 12.5 [160.0] (125.0 – 205.0)	145.2 ± 14.4 [139.0] (79.0 – 211.0)	141.5 ± 11.8 [136.0] (100.0 – 205.0)	148.1 ± 14.9 [135.5] (88.0 – 256.0)	153.7 ± 14.5 [148.0] (97.0 – 237.0)
CHOL (mg/dL) *[p = 0.001]*	79.8 ± 3.7 [79.0] (67.0 – 95.0)	83.0 ± 3.1 [85.0] (68.0 – 97.0)	83.0 ± 4.1 [81.0] (65.0 – 108.0)	90.2 ± 3.7 [89.5] (73.0 – 108.0)	105.2 ± 4.3*** [106.0] (85.0 – 126.0)
TP (g/dL) [p = 0.714]	6.6 ± 0.2 [6.7] (6.1 – 7.5)	6.5 ± 0.2 [6.7] (5.5 – 7.2)	6.6 ± 0.1 [6.7] (6.2 – 6.9)	6.4 ± 0.1 [6.5] (6.0 – 6.9)	6.6 ± 0.1 [6.7] (5.9 – 7.1)
CK (U/L)* [p = 0.305]	293.1 ± 51.5 [255.0] (172.0 – 632.0)	353.8 ± 115.0 [199.0] (109.0 – 1272.0)	346.7 ± 105.4 [235.0] (117.0 – 1224.0)	190.0 ± 17.3* [160.0] (139.0 – 295.0)	357.4 ± 141.7 [235.5] (144.0 – 1626.0)
CREAT (mg/dL)** [p = 0.219]	0.48 ± 0.02 [0.50] (0.40 – 0.50)	0.44 ± 0.03 [0.50] (0.30 – 0.50)	0.49 ± 0.02 [0.50] (0.40 – 0.60)	0.51 ± 0.01 [0.50] (0.50 – 0.60)	0.50 ± 0.03 [0.50] (0.40 – 0.70)
BUN (mg/dL) [p = 0.694]	20.6 ± 1.2 [21.0] (15.0 – 26.0)	20.3 ± 0.9 [20.0] (15.0 – 24.0)	20.0 ± 0.9 [19.5] (17.0 – 25.0)	21.5 ± 0.5 [21.5] (19.0 – 25.0)	21.3 ± 0.8 [21.5] (17.0 – 26.0)

TABLE 30
Clinical Chemistry Parameters of Female Rats Administered Dietary Oxybenzone Continued[a]

Clinical Chemistry Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 8	OXY 3,000 n = 10	OXY 10,000 n = 10	OXY 30,000 n = 10	EE2 0.05 n = 10
GLU (mg/dL)** *[p = 0.026]*	137.4 ± 4.9 [136.0] (118.0 – 161.0)	164.3 ± 12.2 [153.0] (117.0 – 254.0)	134.5 ± 7.8 [135.5] (95.0 – 169.0)	170.9 ± 10.2** [164.0] (138.0 – 251.0)	152.2 ± 8.9 [149.5] (112.0 – 191.0)

Abbreviations: SDH = sorbitol dehydrogenase; TBA = total bile acids; ALB = albumin; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; TRIG = triglycerides; CHOL = cholesterol; TP = total protein; CK = creatine kinase; CREAT = creatinine; BUN = blood urea nitrogen; GLU = glucose

[a]Parametric summary means ± S.E.M. Nonparametric median values are reported in brackets. Numbers in parentheses indicate minimum and maximum nonparametric summary statistic values.
[b]Two pregnant females were excluded from the analysis of the CTRL animals; one female had an unknown mating date while the other was dosed past the protocol specified end date (GD 6).
[c]ANOVA results are presented in brackets for each clinical chemistry parameter analyzed. ANOVA was performed using a nonparametric method with midranks (using the average of left and right ranks for ties) and an unstructured covariance (Brunner et al., 2002). Analysis that indicated significant treatment effects are shown in italics; significance level was set at $p = 0.05$.
Asterisks (*) adjacent to clinical chemistry endpoints in shaded cells indicate significant trends in least square mean comparisons of oxybenzone and controls; the EE2 0.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to mean values in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p \leq 0.01$; ***, $p < 0.001$.

TABLE 31
Clinical Chemistry Parameters of Male Rats Administered Dietary Oxybenzone[a]

Clinical Chemistry Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 9	OXY 3,000 n = 10	OXY 10,000[b] n = 8	OXY 30,000[b] n = 7	EE2 0.05 n = 10
SDH (U/L) [p = 0.711]	7.6 ± 1.8 [6.9] (1.4 – 15.4)	5.5 ± 1.3 [4.2] (2.0 – 15.9)	8.7 ± 2.2 [9.4] (1.4 – 17.3)	5.0 ± 1.3 [4.4] (0.9 – 10.6)	7.4 ± 2.0 [6.9] (1.2 – 21.6)
TBA (µmol/L)* *[p = <0.001]*	48.3 ± 3.7 [47.7] (35.1 – 65.9)	40.4 ± 1.5 [42.1] (33.1 – 46.4)	45.4 ± 4.6 [41.4] (31.0 – 68.1)	60.1 ± 4.7 [59.6] (45.4 – 81.4)	68.7 ± 4.5** [65.7] (53.1 – 94.2)
ALB (g/dL) [p = 0.521]	3.5 ± 0.0 [3.5] (3.4 – 3.6)	3.5 ± 0.0 [3.5] (3.3 – 3.6)	3.5 ± 0.1 [3.6] (3.2 – 3.8)	3.6 ± 0.1 [3.7] (3.4 – 3.9)	3.5 ± 0.0 [3.6] (3.3 – 3.7)
ALT (U/L) *[p = <0.001]*	63.1 ± 1.7 [62.0] (56.0 – 71.0)	63.2 ± 2.9 [62.5] (49.0 – 81.0)	55.4 ± 3.6 [55.0] (45.0 – 68.0)	55.3 ± 4.0 [54.0] (44.0 – 77.0)	81.6 ± 3.3*** [82.5] (65.0 – 97.0)
ALP (U/L) [p = 0.487]	178.3 ± 8.1 [173.0] (150.0 – 215.0)	181.5 ± 11.4 [181.0] (131.0 – 229.0)	180.1 ± 9.4 [179.5] (133.0 – 216.0)	178.7 ± 21.8 [154.0] (131.0 – 290.0)	210.8 ± 16.0 [196.0] (149.0 – 314.0)
AST (U/L)* *[p = 0.020]*	84.6 ± 4.5 [79.0] (72.0 – 114.0)	76.9 ± 3.1 [75.0] (65.0 – 98.0)	72.5 ± 2.1* [72.5] (66.0 – 85.0)	69.9 ± 2.5* [72.0] (61.0 – 78.0)	84.1 ± 5.0 [81.0] (65.0 – 116.0)
TRIG (mg/dL) [p = 0.075]	107.6 ± 8.2 [104.0] (85.0 – 165.0)	106.7 ± 6.7 [108.5] (73.0 – 149.0)	142.6 ± 13.7 [143.0] (102.0 – 215.0)	115.0 ± 16.9 [113.0] (70.0 – 195.0)	86.7 ± 8.2 [90.0] (44.0 – 126.0)
CHOL (mg/dL)* *[p = 0.049]*	97.7 ± 3.5 [95.0] (82.0 – 112.0)	103.3 ± 4.4 [102.5] (90.0 – 136.0)	108.4 ± 3.4 [108.5] (91.0 – 119.0)	112.3 ± 4.7 [111.0] (91.0 – 125.0)	96.0 ± 4.4 [92.0] (80.0 – 120.0)
TP (g/dL)* *[p = 0.035]*	7.0 ± 0.1 [7.1] (6.5 – 7.3)	6.9 ± 0.1 [6.9] (6.6 – 7.4)	7.0 ± 0.1 [7.1] (6.4 – 7.4)	7.3 ± 0.1 [7.2] (7.1 – 7.5)	7.0 ± 0.1 [7.0] (6.7 – 7.3)
CK (U/L) [p = 0.469]	212.4 ± 38.5 [170.0] (111.0 – 432.0)	143.7 ± 15.1 [124.5] (101.0 – 234.0)	167.1 ± 23.4 [154.5] (105.0 – 321.0)	141.0 ± 9.8 [144.0] (109.0 – 167.0)	201.7 ± 31.2 [181.0] (101.0 – 395.0)
CREAT (mg/dL) [p = 0.313]	0.52 ± 0.03 [0.50] (0.40 – 0.60)	0.46 ± 0.02 [0.50] (0.40 – 0.50)	0.48 ± 0.02 [0.50] (0.40 – 0.50)	0.46 ± 0.02 [0.50] (0.40 – 0.50)	0.47 ± 0.02 [0.50] (0.40 – 0.60)
BUN (mg/dL) [p = 0.416]	19.4 ± 1.1 [20.0] (14.0 – 25.0)	20.3 ± 0.7 [20.5] (17.0 – 23.0)	18.6 ± 1.1 [18.5] (15.0 – 23.0)	21.4 ± 0.9 [21.0] (18.0 – 25.0)	19.8 ± 1.0 [21.0] (14.0 – 23.0)

TABLE 31
Clinical Chemistry Parameters of Male Rats Administered Dietary Oxybenzone Continued[a]

Clinical Chemistry Endpoint [ANOVA p value][c]	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[b] n = 9	OXY 3,000 n = 10	OXY 10,000[b] n = 8	OXY 30,000[b] n = 7	EE2 0.05 n = 10
GLU (mg/dL)	177.1 ± 11.9	166.5 ± 10.2	172.4 ± 12.2	170.7 ± 11.5	178.4 ± 12.0
[p = 0.944]	[186.0]	[155.0]	[170.0]	[163.0]	[185.0]
	(123.0 – 244.0)	(139.0 – 243.0)	(117.0 – 230.0)	(130.0 – 217.0)	(122.0 – 234.0)

Abbreviations: SDH = sorbitol dehydrogenase; TBA = total bile acids; ALB = albumin; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; TRIG = triglycerides; CHOL = cholesterol; TP = total protein; CK = creatine kinase; CREAT = creatinine; BUN = blood urea nitrogen; GLU = glucose

[a]Parametric summary means ± S.E.M. Nonparametric median values are reported in brackets. Numbers in parentheses indicate minimum and maximum nonparametric summary statistic values.
[b]A total of six males were excluded from the analysis; all had either unknown/undetermined mating dates.
[c]ANOVA results are presented in brackets for each clinical chemistry parameter analyzed. ANOVA was performed using a nonparametric method with midranks (using the average of left and right ranks for ties) and an unstructured covariance (Brunner et al., 2002). Analysis that indicated significant treatment effects are shown in italics; significance level was set at $p = 0.05$.
Asterisks (*) adjacent to clinical chemistry endpoints in shaded cells indicate significant trends in least square mean comparisons of oxybenzone and controls; the EE20.05 ppm treatment group was excluded from analysis of trend. Asterisks adjacent to mean values in shaded cells indicate significant pairwise differences from controls as determined by Dunnett's method for adjusted contrasts. *, $p < 0.05$; **, $p < 0.01$; ***, $p \leq 0.001$.

TABLE 32
Hormone Levels of Male Rats Administered Dietary Oxybenzone[a,b]

Hormone Levels	Oxybenzone (ppm)				Ethinyl Estradiol (ppm)
	CTRL[c] n = 9	**OXY 3,000** n = 10	**OXY 10,000[c]** n = 8	**OXY 30,000[c]** n = 7	**EE2 0.05[g]** n = 10
Testosterone[d,e] (ng/ml)	1.9 ± 0.4 [1.8] (0.6 – 5.1)	2.7 ± 1.2 [1.3] (0.7 – 13.0)	3.6 ± 1.3 [2.5] (1.0 – 12.0)	4.5 ± 2.2 [1.5] (1.1 – 15.9)	3.1 ± 0.7 [2.6] (0.8 – 7.3)
FSH[d,f] (ng/ml)	15.7 ± 1.2 [14.4] (13.1 – 24.2)	16.8 ± 0.9 [16.3] (13.3 – 22.7)	14.8 ± 1.0 [13.9] (11.8 – 20.6)	16.8 ± 0.8 [16.4] 14.1 – 19.2)	16.1 ± 07[g] [15.5] (14.3 – 20.9)

Abbreviations: FSH = follicle stimulating hormone

[a]Parametric summary means ± S.E.M. Nonparametric median values are reported in brackets. Numbers in parentheses indicate minimum and maximum nonparametric summary statistic values.
[b]Luteinizing hormone levels were below the limit of quantification and were not included in the analysis.
[c]A total of six males were excluded from the analysis; all had either unknown/undetermined mating dates.
[d]ANOVA was performed using a nonparametric method with midranks (using the average of left and right ranks for ties) and an unstructured covariance (Brunner et al., 2002).
[e]ANOVA results: Treatment, p = 0.381.
[f]ANOVA results: Treatment, p = 0.200.
[g]One male in the EE2 0.05 ppm treatment group was excluded from the analysis of FSH levels (n = 9). The FSH level for this male was reported as >100.0 ng/ml.
Pairwise comparisons were performed with Dunnett's method for adjusted contrasts. Tests were conducted as two-sided at the 0.05 significance level; no significant trends or pairwise differences were observed between control and treatment groups.

TABLE 33
Histopathological Evaluation of the Mammary Glands in Female Rats Administered Dietary Oxybenzone

Integumentary System		
	CTRL	**OXY 30,000 ppm**
Mammary Gland, Alveolus, Hyperplasia		
Incidence[a]	1/25 (4.0%)	2/25 (8.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	0|1|0|0	0|1|0|1
Severity Significance[d]	-	-

[a]Data are presented as incidence (number of animals with lesion/number of animals examined). Numbers in parentheses represent the percentage identified with lesions.
[b]Statistical significance, or lack of significance "-", is shown. The exact Cochran-Armitage trend test was used to test for trends and the Fisher's exact test was used to compare incidences between dosed groups and the control group; tests were performed as one-sided. The CTRL column contains the result of the trend test.
[c]Severity profile represents the number of animals with lesions graded as minimal/mild/moderate/marked.
[d]Statistical significance, or lack of significance "-", is shown. The Jonckheere-Terpstra (JT) test was used to test for trends and Shirley's method modified by Williams (JT-SW) was used for comparison of dosed groups to control. The CTRL column contains the result of the trend test.

TABLE 34
Histopathological Evaluation of the Mammary Glands in Male Rats Administered Dietary Oxybenzone

Integumentary System				
	CTRL	**OXY 3,000 ppm**	**OXY 10,000 ppm**	**OXY 30,000 ppm**
Mammary Gland, Alveolus, Hyperplasia				
Incidence[a]	2/25 (8.0%)	5/25 (20.0%)	7/25 (28.0%)	2/25 (8.0%)
Incidence Significance[b]	-	-	-	-
Severity Profile[c]	1|1|0|0	4|1|0|0	4|3|0|0	1|1|0|0
Severity Significance[d]	-	*	-	-

[a]Data are presented as incidence (number of animals with lesion/number of animals examined). Numbers in parentheses represent the percentage identified with lesions.
[b]Statistical significance, or lack of significance "-", is shown. The exact Cochran-Armitage trend test was used to test for trends and the Fisher's exact test was used to compare incidences between dosed groups and the control group; tests were performed as one-sided. The CTRL column contains the result of the trend test.
[c]Severity profile represents the number of animals with lesions graded as minimal/mild/moderate/marked.
[d]Statistical significance, or lack of significance "-", is shown. The Jonckheere-Terpstra (JT) test was used to test for trends and Shirley's method modified by Williams (JT-SW) was used for comparison of dosed groups to control. The CTRL column contains the result of the trend test. Significant results are indicated in gray. *, $p = <0.05$.

TABLE 35
Histopathological Evaluation of Tissues/Organs in Male Rats Administered Dietary Oxybenzone

Endocrine System		
	CTRL	**OXY 30,000 ppm**
Pituitary Gland, Pars Distalis: Cyst		
Incidence[a]	2/25 (8.0%)	1/25 (4.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	2|0|0|0	1|0|0|0
Severity Significance[d]	-	-
Thyroid Gland: Ultimobranchial Cyst		
Incidence[a]	2/25 (8.0%)	7/25 (28.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	2|0|0|0	5|2|0|0
Severity Significance[d]	*	*

[a]Data are presented as incidence (number of animals with lesion/number of animals examined). Numbers in parentheses represent the percentage identified with lesions.
[b]Statistical significance, or lack of significance "-", is shown. The exact Cochran-Armitage trend test was used to test for trends and the Fisher's exact test was used to compare incidences between dosed groups and the control group; tests were performed as one-sided. The CTRL column contains the result of the trend test.
[c]Severity profile represents the number of animals with lesions graded as minimal/mild/moderate/marked.
[d]Statistical significance, or lack of significance "-", is shown. The Jonckheere-Terpstra (JT) test was used to test for trends and Shirley's method modified by Williams (JT-SW) was used for comparison of dosed groups to control. The CTRL column contains the result of the trend test. Significant results are indicated in gray. *, $p = <0.05$.

TABLE 36
Histopathological Evaluation of Mammary Glands and Tissues/Organs in Male Rats Administered Dietary Ethinyl Estradiol

	CTRL	EE2 0.05 ppm
Endocrine System		
Pituitary Gland, Pars Distalis: Cyst		
Incidence[a]	2/25 (8.0%)	0/25 (0.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	2|0|0|0	0|0|0|0
Severity Significance[d]	-	-
Thyroid Gland: Ultimobranchial Cyst		
Incidence[a]	2/25 (8.0%)	7/25 (28.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	2|0|0|0	6|1|0|0
Severity Significance[d]	*	*
Genital System		
Prostate –Ventral Lobe: Infiltration Cellular, Lymphocyte		
Incidence[a]	1/25 (4.0%)	3/25 (12.0%)
Incidence Significance[b]	-	-
Severity Profile[c]	1|0|0|0	3|0|0|0
Severity Significance[d]	-	-
Integumentary System		
Mammary Gland, Alveolus, Hyperplasia		
Incidence[a]	2/25 (8.0%)	10/25 (40.0%)
Incidence Significance[b]	*	**
Severity Profile[c]	1|1|0|0	5|5|0|0
Severity Significance[d]	**	**

[a]Data are presented as incidence (number of animals with lesion/number of animals examined). Numbers in parentheses represent the percentage identified with lesions.
[b]Statistical significance, or lack of significance "-", is shown. The exact Cochran-Armitage trend test was used to test for trends and the Fisher's exact test was used to compare incidences between dosed groups and the control group; tests were performed as one-sided. The CTRL column contains the result of the trend test. Significant results are indicated in gray. *, $p = <0.05$.
[c]Severity profile represents the number of animals with lesions graded as minimal/mild/moderate/marked.
[d]Statistical significance, or lack of significance "-", is shown. The Jonckheere-Terpstra (JT) test was used to test for trends and Shirley's method modified by Williams (JT-SW) was used for comparison of dosed groups to control. The CTRL column contains the result of the trend test. Significant results are indicated in gray. *, $p = <0.05$; **, $p \leq 0.01$.