C Number:	R10997
Study Gender:	Both
PWG Approval Date	See web page for date of PWG Approval

Study Number: R10997
Test Type: RACB
Route: Dosing in Feed
Species/Strain: Rat/Sprague-Dawley

R16: Pubertal Markers Summary
Test Compound: Diisobutyl Phthalate
CAS Number: 84-69-5

Date Report Requested: 03/27/2019
Time Report Requested: 10:37:02
Lab: RTI

Male

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	All Males	No. Examined (litters)	91 (21)	72 (20)	86 (19)	79 (18)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining BPS (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of BPS				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	45.4 ± 0.5 **	45.0 ± 0.5	45.8 ± 0.3	49.2 ± 0.6 **
			Litter Mean of Adjusted ± SE[e]	46.4 ± 0.3 **	45.4 ± 0.4	45.9 ± 0.3	47.9 ± 0.3 *
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p=0.008	p=0.225	p=0.225	p=0.212
			BW at Attainment (g)[h]	194.6 ± 1.7	188.5 ± 2.8	191.5 ± 2.8	190.5 ± 2.8
			BW at Weaning (g)[h]	51.0 ± 1.2 **	48.3 ± 1.4	46.7 ± 1.7	40.1 ± 1.4 **

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Male

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	F1c NonParent Males	No. Examined (litters)	45 (17)	31 (13)	39 (17)	39 (15)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining BPS (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of BPS				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	45.7 ± 0.6 **	45.3 ± 0.6	45.9 ± 0.4	48.4 ± 0.5 **
			Litter Mean of Adjusted ± SE[e]	46.6 ± 0.5	45.4 ± 0.7	45.6 ± 0.4	47.6 ± 0.4
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p=0.049	p=0.245	p=0.184	p=0.385
			BW at Attainment (g)[h]	196.6 ± 2.9	190.4 ± 4.4	188.3 ± 2.9	194.1 ± 2.6
			BW at Weaning (g)[h]	50.9 ± 1.5 **	46.8 ± 1.6	44.5 ± 1.2 **	42.1 ± 1.0 **

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Male

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	F1c Parental Males	No. Examined (litters)	40 (21)	40 (20)	40 (19)	40 (18)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining BPS (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of BPS				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	45.2 ± 0.6 **	44.7 ± 0.5	45.6 ± 0.4	49.4 ± 0.6 **
			Litter Mean of Adjusted ± SE[e]	46.3 ± 0.4 **	45.2 ± 0.4	45.7 ± 0.4	47.7 ± 0.3
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p=0.007	p=0.461	p=0.572	p=0.253
			BW at Attainment (g)[h]	193.8 ± 2.0	187.8 ± 3.1	192.9 ± 2.7	189.7 ± 2.9
			BW at Weaning (g)[h]	51.2 ± 1.2 **	48.9 ± 1.5	47.2 ± 1.6	39.5 ± 1.4 **

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Female

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	All Females	No. Examined (litters)	69 (20)	81 (19)	89 (20)	74 (18)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining VO (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of VO				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	34.0 ± 0.4 **	35.7 ± 0.5 *	36.5 ± 0.4 **	37.9 ± 0.4 **
			Litter Mean of Adjusted ± SE[e]	34.5 ± 0.4 **	35.9 ± 0.5	36.6 ± 0.4 **	37.3 ± 0.4 **
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p<0.001	p=0.038	p<0.001	p<0.001
			BW at Attainment (g)[h]	107.9 ± 2.7	113.2 ± 3.0	116.3 ± 2.1	108.4 ± 2.3
			BW at Weaning (g)[h]	48.7 ± 1.3 **	46.0 ± 1.3	44.6 ± 1.4	37.8 ± 1.1 **

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Female

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	F1c NonParent Female	No. Examined (litters)	28 (15)	32 (12)	40 (17)	32 (13)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining VO (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of VO				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	34.4 ± 0.6 **	35.6 ± 0.7	36.1 ± 0.5 *	38.4 ± 0.4 **
			Litter Mean of Adjusted ± SE[e]	34.4 ± 0.6 **	35.6 ± 0.7	36.1 ± 0.5 *	38.4 ± 0.4 **
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p<0.001	p=0.162	p=0.028	p<0.001
			BW at Attainment (g)[h]	107.6 ± 4.0	113.6 ± 4.4	114.8 ± 2.7	111.0 ± 2.3
			BW at Weaning (g)[h]	47.3 ± 1.4 **	46.5 ± 1.6	44.4 ± 1.7	37.6 ± 0.8 **

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Female

Generation	Litter	Cohort		Treatment Groups (ppm)			
				0	1000	5000	10000
F1	C	F1c Parental Females	No. Examined (litters)	40 (20)	40 (19)	40 (20)	40 (18)
			No. Removed (litters)[a]	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining VO (litters)[b]	0 (0)	0 (0)	0 (0)	0 (0)
			Day of VO				
			Mean Analysis[c]				
			Litter Mean ± SE[d]	33.6 ± 0.4 **	35.6 ± 0.6 *	36.7 ± 0.6 **	37.7 ± 0.4 **
			Litter Mean of Adjusted ± SE[e]	34.4 ± 0.4 *	35.9 ± 0.6	36.7 ± 0.5 **	36.6 ± 0.4 *
			Proportional Hazards Analysis[f]				
			Litter-based Model[g]	p<0.001	p=0.031	p<0.001	p=0.001
			BW at Attainment (g)[h]	106.7 ± 2.9	112.4 ± 2.8	115.9 ± 2.7 *	107.6 ± 2.7
			BW at Weaning (g)[h]	49.1 ± 1.3 **	46.4 ± 1.5	44.7 ± 1.5	37.6 ± 1.2 **

LEGEND

BPS = Balanopreputial separation; BW = Body weight; VO = Vaginal opening

In multiple breeding/littering studies Litter A is the default designation for the first litter; subsequent litters would be B, C etc.

The All Males cohort includes all the F1c NonParent Males and F1c Parental Males cohorts and did not include the F1c MGWM Males or any males that were weaned and not assigned to a cohort. The All Females cohort includes all the F1c NonParent Female and F1c Parental Females cohorts and did not include any females that were weaned and not assigned to a cohort..

No. Examined (litters) = the number of animals or pups examined (number of litters represented)

[a]Animals that died or were removed prior to the end of the observation period and did not attain. These animals were excluded from all analyses.

[b]Animals that survived to the end of the observation period without attaining.

[c]Summary statistics and mixed model results are presented for animals that attained during the observation period.

[d]Means of litter means presented. Trend and pairwise tests were based on mixed models for day of attainment with dose as a covariate and a random effect for litter. The Dunnett-Hsu adjustment was used for multiple comparisons.

[e]Mean adjusted day of attainment was calculated from the mean of the litter means of the weaning weight-adjusted attainment days for individual pups. Trend and pairwise tests were based on mixed models for day of attainment with dose and weaning weight as covariates and a random effect for litter. The Dunnett-Hsu adjustment was used for multiple comparisons.

[f]Animals that did not attain by the end of the observation period were included in the proportional hazards analysis.

[g]P-values for trend and pairwise comparisons were calculated from a Cox proportional hazards model with dose and weaning weight as covariates and a random effect for litter, and a Hommel adjustment for multiple comparisons.

[h]Analysis of body weight at attainment and body weight at weaning were performed using mixed effects models with dose as covariate and a random effect for litter. The Dunnett-Hsu adjustment was used for multiple comparisons. Animals that attained during the observation period were used for analysis.

Statistical significance for the control group indicates a significant trend test

Statistical significance for a treatment group indicates a significant pairwise test compared to the vehicle control group

* Statistically significant at P <= 0.05

** Statistically significant at P <= 0.01

** END OF REPORT **