

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

R14: Developmental Markers Summary
Test Compound: Diisobutyl Phthalate
CAS Number: 84-69-5

Date Report Requested: 03/27/2019
Time Report Requested: 10:08:50
Lab: RTI

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

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			F1 Male				
Generation	Litter	Cohort	Treatment Groups (ppm)				
			0	1000	5000	10000	
F1	C		PND 13				
		All Males	No. Examined (litters)	101 (21)	75 (20)	94 (19)	88 (19)
			No. of areolae/nipples per litter ^a	0.00 ± 0.00 **	0.00 ± 0.00	0.00 ± 0.00	0.46 ± 0.17 **
			No. pups with areolae/nipples (%) ^b	0 (0.00) **	0 (0.00)	0 (0.00)	14 (15.91) **
			No. litters with areolae/nipples (%) ^b	0 (0.00) **	0 (0.00)	0 (0.00)	8 (42.11) **
			Testicular Descent				
			No. Examined (litters)	101 (21)	75 (20)	94 (19)	88 (19)
			No. Removed (litters) ^c	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters) ^d	0 (0)	0 (0)	0 (0)	0 (0)
			Day of Testes Descent				
			Mean Analysis ^e				
			Litter Mean ± SE ^f	16.6 ± 0.2	16.3 ± 0.2	15.9 ± 0.2 *	16.5 ± 0.3
			Proportional Hazards Analysis ^g				
			Litter-based Model ^h	p=0.789	p=0.607	p=0.088	p=0.936

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Treatment Groups (ppm)

Generation	Litter	Cohort	Treatment Groups (ppm)				
			0	1000	5000	10000	
F1	C	F1c NonParent Males	PND 13				
			No. Examined (litters)	45 (17)	31 (13)	39 (17)	39 (15)
			No. of areolae/nipples per litter ^a	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
			No. pups with areolae/nipples (%) ^b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		No. litters with areolae/nipples (%) ^b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
		Testicular Descent					
		No. Examined (litters)	45 (17)	31 (13)	39 (17)	40 (16)	
		No. Removed (litters) ^c	0 (0)	0 (0)	0 (0)	0 (0)	
		No. Not Attaining Testes Descent (litters) ^d	0 (0)	0 (0)	0 (0)	0 (0)	
		Day of Testes Descent					
		Mean Analysis ^e					
		Litter Mean ± SE ^f	16.6 ± 0.2	16.4 ± 0.3	15.9 ± 0.3	16.4 ± 0.3	
		Proportional Hazards Analysis ^g					
Litter-based Model ^h	p=0.353	p=0.825	p=0.301	p=0.825			

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F1 Male

Generation	Litter	Cohort	Treatment Groups (ppm)			
			0	1000	5000	10000
F1	C	F1c Parental Males	PND 13			
		No. Examined (litters)	40 (21)	40 (20)	37 (19)	40 (18)
		No. of areolae/nipples per litter ^a	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
		No. pups with areolae/nipples (%) ^b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		No. litters with areolae/nipples (%) ^b	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		Testicular Descent				
		No. Examined (litters)	40 (21)	40 (20)	40 (19)	40 (18)
		No. Removed (litters) ^c	0 (0)	0 (0)	0 (0)	0 (0)
		No. Not Attaining Testes Descent (litters) ^d	0 (0)	0 (0)	0 (0)	0 (0)
		Day of Testes Descent				
		Mean Analysis ^e				
		Litter Mean ± SE ^f	16.7 ± 0.2	16.3 ± 0.2	15.9 ± 0.2 *	16.5 ± 0.3
		Proportional Hazards Analysis ^g				
		Litter-based Model ^h	p=0.198	p=0.450	p=0.083	p=0.450

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			F2 Male				
Generation	Litter	Cohort	Treatment Groups (ppm)				
			0	1000	5000	10000	
F2	C		PND 13				
		All Males	No. Examined (litters)	161 (31)	161 (35)	135 (27)	122 (33)
			No. of areolae/nipples per litter ^a	0.00 ± 0.00 **	0.00 ± 0.00	0.35 ± 0.18 *	1.63 ± 0.38 **
			No. pups with areolae/nipples (%) ^b	0 (0.00) **	0 (0.00)	11 (8.15) *	48 (39.34) **
			No. litters with areolae/nipples (%) ^b	0 (0.00) **	0 (0.00)	7 (25.93) **	19 (57.58) **
			Testicular Descent				
			No. Examined (litters)	161 (31)	161 (35)	135 (27)	122 (33)
			No. Removed (litters) ^c	0 (0)	0 (0)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters) ^d	1 (1)	2 (2)	2 (2)	10 (7)
			Day of Testes Descent				
			Mean Analysis ^e				
			Litter Mean ± SE ^f	15.5 ± 0.2 **	15.5 ± 0.2	15.0 ± 0.2	14.7 ± 0.2 *
			Proportional Hazards Analysis ^g				
			Litter-based Model ^h	p=0.041	p=0.764	p=0.764	p=0.596

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LEGEND

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

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

The number of areolae/nipples per litter are shown as mean \pm SEM

No. of pups with areolae/ nipples reported as number of affected pups (%)

No. of litters with areolae/ nipples reported as number of affected litters (%)

If measured, the No. of areolae/nipples at terminal sacrifice are shown as mean \pm SEM

^aStatistical analysis for the F1 generation performed by Jonckheere (trend) and Shirley or Dunn (pairwise) tests. Statistical analysis for the F2 generation performed using a bootstrapped Jonckheere trend test; pairwise comparisons were done using the Datta-Satten modified Wilcoxon tests with Hommel adjustment for multiple comparisons.

^bStatistical analysis for the F1 generation was performed using Cochran-Armitage (trend) and Fisher Exact (pairwise) tests. Statistical analysis for the F2 generation was performed using a Rao-Scott Cochran-Armitage test for both trend and pairwise tests.

^cAnimals that died or were removed prior to the end of the observation period and did not attain. These animals were excluded from all analyses.

^dAnimals that survived to the end of the observation period without attaining.

^eSummary statistics and mixed model results are presented for animals that attained during the observation period.

^fMeans 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.

^gAnimals that did not attain by the end of the observation period were included in the proportional hazards analysis.

^hP-values for trend and pairwise comparisons were calculated from a Cox proportional hazards model with random effect for litter and a Hommel adjustment for multiple comparisons.

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 $P \leq 0.05$

** Statistically significant at $P \leq 0.01$

**** END OF REPORT ****