Study Number: R92025B

Test Type: RACB

Route: Dosing in Feed

Species/Strain: Rat/Sprague-Dawley

R14: Developmental Markers Summary

Test Compound: 4-Methylimidazole

CAS Number: 822-36-6

Date Report Requested: 02/12/2019

Time Report Requested: 10:05:33

Lab: RTI

C Number: R92025B

Study Gender: Both

PWG Approval Date   See web page for date of PWG Approval

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F1 Male

				Treatment Groups (ppm)		
Generation	Litter	Cohort		0	750	2500
F1	C		**PND 13**			
		All Males	No. Examined (litters)	99 (18)	115 (22)	61 (15)
			No. of areolae/nipples per litter[a]	0.00 ± 0.00	0.00 ± 0.00	0.14 ± 0.10
			No. pups with areolae/nipples (%)[b]	0 (0 .00) *	0 (0 .00)	3 (4 .92)
			No. litters with areolae/nipples (%)[b]	0 (0 .00)	0 (0 .00)	2 (13.33)
			Testicular Descent			
			No. Examined (litters)	99 (18)	114 (22)	60 (15)
			No. Removed (litters)[c]	0 (0)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters)[d]	0 (0)	1 (1)	0 (0)
			Day of Testes Descent			
			Mean Analysis[e]			
			Litter Mean ± SE[f]	16.7 ± 0.2 *	16.8 ± 0.2	17.1 ± 0.2
			Proportional Hazards Analysis[g]			
			Individual Median Day of Testes Descent[h]	17 *	17	17
			Litter-based Model[i]	p=0.047	p=0.728	p=0.202

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F1 Male

				Treatment Groups (ppm)		
Generation	**Litter**	**Cohort**		**0**	**750**	**2500**
F1	**C**		**PND 13**			
		F1 NonParental Male	No. Examined (litters)	49 (18)	56 (22)	20 (8)
			No. of areolae/nipples per litter[a]	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)
			No. litters with areolae/nipples (%)[b]	0 (0 .00)	0 (0 .00)	0 (0 .00)
			Testicular Descent			
			No. Examined (litters)	49 (18)	56 (22)	20 (8)
			No. Removed (litters)[c]	0 (0)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters)[d]	0 (0)	0 (0)	0 (0)
			Day of Testes Descent			
			Mean Analysis[e]			
			Litter Mean ± SE[f]	16.9 ± 0.3	16.8 ± 0.2	17.1 ± 0.2
			Proportional Hazards Analysis[g]			
			Individual Median Day of Testes Descent[h]	17	17	17
			Litter-based Model[i]	p=0.126	p=0.756	p=0.683

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F1 Male

			Treatment Groups (ppm)		
Generation	Litter	Cohort	0	750	2500
F1	C		**PND 13**		
		F1 Parental Males	No. Examined (litters)		
			40 (18)	44 (22)	39 (15)
			No. of areolae/nipples per litter[a]		
			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)
			No. litters with areolae/nipples (%)[b]		
			0 (0 .00)	0 (0 .00)	0 (0 .00)
			Testicular Descent		
			No. Examined (litters)		
			40 (18)	44 (22)	40 (15)
			No. Removed (litters)[c]		
			0 (0)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters)[d]		
			0 (0)	0 (0)	0 (0)
			Day of Testes Descent		
			Mean Analysis[e]		
			Litter Mean ± SE[f]		
			16.6 ± 0.2 *	16.9 ± 0.3	17.2 ± 0.2
			Proportional Hazards Analysis[g]		
			Individual Median Day of Testes Descent[h]		
			17 *	17	17 *
			Litter-based Model[i]		
			p=0.020	p=0.431	p=0.077

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F2 Male

				Treatment Groups (ppm)		
Generation	Litter	Cohort		0	750	2500
F2	C		**PND 13**			
		All Males	No. Examined (litters)	108 (25)	133 (32)	69 (20)
			No. of areolae/nipples per litter[a]	0.00 ± 0.00	0.00 ± 0.00	0.17 ± 0.17
			No. pups with areolae/nipples (%)[b]	0 (0 .00)	0 (0 .00)	3 (4 .35)
			No. litters with areolae/nipples (%)[b]	0 (0 .00)	0 (0 .00)	1 (5 .00)
			Testicular Descent			
			No. Examined (litters)	107 (25)	132 (32)	68 (20)
			No. Removed (litters)[c]	1 (1)	0 (0)	0 (0)
			No. Not Attaining Testes Descent (litters)[d]	0 (0)	0 (0)	1 (1)
			Day of Testes Descent			
			Mean Analysis[e]			
			Litter Mean ± SE[f]	18.1 ± 0.3 **	18.5 ± 0.4	19.4 ± 0.4 *
			Proportional Hazards Analysis[g]			
			Individual Median Day of Testes Descent[h]	18 **	19 *	20 **
			Litter-based Model[i]	p=0.001	p=0.458	p=0.012

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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 ± 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 ± SEM

[a]Statistical 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.

[b]Statistical 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.

[c]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.

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

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

[f]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.

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

[h]Individual medians and trend and pairwise comparisons were calculated from a Cox proportional hazards model with dose as a covariate. The Hommel adjustment was used for multiple comparisons.

[i]P-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.

* Statistically significant at P <= 0.05

** Statistically significant at P <= 0.01

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

** END OF REPORT **