

**Study Number:** R16011D

**Test Type:** Teratology

**Route:** Oral Gavage

**Species/Strain:** Rabbit/New Zealand White

**C Number:**

**Study Gender:**

**PWG Approval Date**

**R10: Fetal Defects**

**Test Compound:** 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine

**CAS Number:** 95737-68-1

R16011D

Female

See web page for date of PWG Approval

**Date Report Requested:** 10/22/2019

**Time Report Requested:** 12:37:28

**Lab:** Southern Research

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**F0 Female: Main Study Animals**

	Classification	Treatment Groups (mg/kg/day)			
		0	62.5	125	250
Total number of fetuses examined		214	185	193	136
	<b>External</b>				
No. Fetuses examined		214	185	193	136
No. Litters examined		24	23	22	16
<b>Extremities</b>					
Tail, Bent	Malformation	1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
<b>Mouth/Face</b>					
Face, Cyst	Variation	1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
<b>Trunk</b>					
General, Umbilical hernia	Malformation	0 (0.00)	1 (0.54)	0 (0.00)	0 (0.00)
		0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)

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	0	62.5	125	250
<b>Visceral</b>				
No. Fetuses examined	214	185	193	136
No. Litters examined	24	23	22	16
<b>Abdominal Viscera</b>				
Intestine, colon, Kinked	Variation	1 (0.47)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)
Stomach, Distended	Malformation	1 (0.47)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)
<b>Major Vessels</b>				
Aortic arch, Malpositioned	Malformation	1 (0.47)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)
Subclavian artery, right, Absent	Variation	1 (0.47)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)
<b>Reproductive Tract</b>				
Epididymis, left, Absent	Malformation	0 (0.00)	0 (0.00)	1 (0.52)
		0 (0.00)	0 (0.00)	1 (4.55)
Testis, left, Absent	Malformation	0 (0.00)	0 (0.00)	2 (1.04)
		0 (0.00)	0 (0.00)	2 (9.09)
Testis, left, Malpositioned	Malformation	1 (0.47)	1 (0.54)	0 (0.00)
		1 (4.17)	1 (4.35)	0 (0.00)
Testis, right, Absent	Malformation	0 (0.00)	0 (0.00)	1 (0.52)
		0 (0.00)	0 (0.00)	1 (4.55)
Testis, right, Malpositioned	Malformation	0 (0.00)	0 (0.00)	1 (0.52)
		0 (0.00)	0 (0.00)	1 (4.55)
<b>Thoracic Viscera</b>				
Lung lobe, accessory, Absent	Malformation	1 (0.47)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)
Lung lobe, left caudal, Absent	Malformation	1 (0.47)	0 (0.00)	0 (0.00)

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F0 Female: Main Study Animals

	Classification	Treatment Groups (mg/kg/day)			
		0	62.5	125	250
Lung lobe, right caudal, Absent	Malformation	1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)
Thymus, Supernumerary	Variation	1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
		5 (2.34)	2 (1.08)	2 (1.04)	2 (1.47)
		3 (12.50)	2 (8.70)	2 (9.09)	2 (12.50)
<b>Urinary Tract</b>					
Kidney, left, Absent	Malformation	1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Kidney, right, Hydronephrosis	Malformation	0 (0.00)	1 (0.54)	0 (0.00)	0 (0.00)
		0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
<b>Head - Rabbit</b>					
No. Fetuses examined		214	185	191	134
No. Litters examined		24	23	22	16
<b>Brain</b>					
Ventricles, Hydrocephaly	Malformation	0 (0.00)	0 (0.00)	1 (0.52)	0 (0.00)
		0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
<b>Eyes</b>					
Eye, right, Ocular coloboma	Malformation	1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)

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F0 Female: Main Study Animals

Classification	Treatment Groups (mg/kg/day)				
	0	62.5	125	250	
<b>Skeletal</b>					
No. Fetuses examined	214	185	193	136	
No. Litters examined	24	23	22	16	
<b>Ribs</b>					
Costal cartilage, 7th bilateral, Not fused to sternum	Malformation	0 (0.00)	0 (0.00)	0 (0.00)	3 (2.21)
		0 (0.00)	0 (0.00)	0 (0.00)	1 (6.25)
Costal cartilage, 7th left, Not fused to sternum	Malformation	0 (0.00)	0 (0.00)	2 (1.05)	0 (0.00)
		0 (0.00)	0 (0.00)	2 (9.09)	0 (0.00)
Costal cartilage, 7th right, Not fused to sternum	Malformation	0 (0.00)	0 (0.00)	1 (0.53)	0 (0.00)
		0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Costal cartilage, 7th unilateral or bilateral, Not fused to sternum	Malformation	0 (0.00)	0 (0.00)	3 (1.58)	3 (2.21)
		0 (0.00)	0 (0.00)	2 (9.09)	1 (6.25)
Costal cartilage, 8th bilateral, Fused to sternum	Malformation	1 (0.48)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Costal cartilage, 8th left, Fused to sternum	Malformation	1 (0.48)	0 (0.00)	0 (0.00)	0 (0.00)
		1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Rib, 13th bilateral, Detached	Variation	0 (0.00)	0 (0.00)	1 (0.53)	0 (0.00)
		0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Rib, 13th bilateral, Short	Variation	3 (1.44)	3 (1.62)	4 (2.11)	0 (0.00)
		1 (4.17)	2 (8.70)	4 (18.18)	0 (0.00)
Rib, 13th left, Detached	Variation	1 (0.48)	4 (2.16)	10 (5.26) #	2 (1.47)
		1 (4.17)	3 (13.04)	7 (31.82)	2 (12.50)
Rib, 13th left, Short	Variation	8 (3.85)	9 (4.86)	12 (6.32)	2 (1.47)
		6 (25.00)	8 (34.78)	10 (45.45)	2 (12.50)
Rib, 13th left, Unossified	Variation	0 (0.00)	1 (0.54)	0 (0.00)	0 (0.00)
		0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
Rib, 13th left, Unpaired	Variation	19 (9.13)	16 (8.65)	13 (6.84)	8 (5.88)
		14 (58.33)	12 (52.17)	10 (45.45)	5 (31.25)

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F0 Female: Main Study Animals

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		0	62.5	125	250
Rib, 13th right, Detached	Variation	4 (1.92) 4 (16.67)	5 (2.70) 4 (17.39)	6 (3.16) 5 (22.73)	2 (1.47) 2 (12.50)
Rib, 13th right, Interrupted	Variation	0 (0.00) 0 (0.00)	1 (0.54) 1 (4.35)	0 (0.00) 0 (0.00)	1 (0.74) 1 (6.25)
Rib, 13th right, Short	Variation	6 (2.88) 5 (20.83)	13 (7.03) 7 (30.43)	13 (6.84) 10 (45.45)	11 (8.09) 8 (50.00)
Rib, 13th right, Unpaired	Variation	17 (8.17) 13 (54.17)	10 (5.41) 7 (30.43)	14 (7.37) 10 (45.45)	13 (9.56) 10 (62.50)
Rib, 1st left, Interrupted	Variation	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	1 (0.74) 1 (6.25)
Rib, 1st left, Unossified	Variation	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	1 (0.74) 1 (6.25)
<b>Skull</b>					
General, Enlarged fontanel	Variation	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	1 (0.74) 1 (6.25)
General, Supernumerary ossification site	Variation	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	1 (0.74) 1 (6.25)
Interfrontal suture, Supernumerary ossification site	Variation	0 (0.00) 0 (0.00)	1 (0.54) 1 (4.35)	1 (0.52) 1 (4.55)	0 (0.00) 0 (0.00)
Interparietal suture, Supernumerary ossification site	Variation	1 (0.47) 1 (4.17)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)
Parietal, bilateral, Additional Suture	Variation	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	6 (3.11) 1 (4.55)	0 (0.00) 0 (0.00)
Parietal, left, Additional Suture	Variation	0 (0.00) 0 (0.00)	1 (0.54) 1 (4.35)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)
<b>Sternebrae</b>					
Sternebra, 1st, Supernumerary site	Variation	1 (0.48) 1 (4.17)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)	0 (0.00) 0 (0.00)
Sternebra, 2nd, Misaligned	Variation	0 (0.00)	1 (0.54)	0 (0.00)	0 (0.00)

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Sternebra, 4th, Fused	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)
	1 (0.48)	1 (0.54)	2 (1.04)	1 (0.74)
	1 (4.17)	1 (4.35)	2 (9.09)	1 (6.25)
Sternebra, 5th, Incomplete ossification	1 (0.48)	0 (0.00)	0 (0.00)	0 (0.00)
	1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Sternebra, 5th, Unossified	1 (0.48)	0 (0.00)	4 (2.08)	0 (0.00)
	1 (4.17)	0 (0.00)	2 (9.09)	0 (0.00)
Sternebra, 6th, Incomplete ossification	0 (0.00)	0 (0.00)	2 (1.04)	0 (0.00)
	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
Sternebra, 6th, Incomplete ossification, Minimal	1 (0.48)	0 (0.00)	0 (0.00)	0 (0.00)
	1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Sternebra, 6th, Unossified	4 (1.90)	4 (2.16)	11 (5.73)	1 (0.74)
	3 (12.50)	4 (17.39)	8 (36.36)	1 (6.25)
Sternebra, 6th, decreases in ossification	5 (2.38)	4 (2.16)	13 (6.77)	1 (0.74)
	4 (16.67)	4 (17.39)	8 (36.36)	1 (6.25)
Sternebra, between sternebra, Supernumerary site	1 (0.48)	0 (0.00)	0 (0.00)	0 (0.00)
	1 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)
Sternebra, multiple sites, Fused	0 (0.00)	1 (0.54)	0 (0.00)	1 (0.74)
	0 (0.00)	1 (4.35)	0 (0.00)	1 (6.25)
Sternebra, multiple sites, Unossified	0 (0.00)	1 (0.54)	1 (0.52)	0 (0.00)
	0 (0.00)	1 (4.35)	1 (4.55)	0 (0.00)
<b>Supernumerary Rib</b>				
Thoracolumbar, left, Full	0 (0.00)	0 (0.00)	1 (0.52)	0 (0.00)
	0 (0.00)	0 (0.00)	1 (4.55)	0 (0.00)
<b>Vertebrae</b>				
Lumbar vertebra, 7th, Fused to ilium	6 (2.80)	2 (1.08)	5 (2.59)	7 (5.15)
	5 (20.83)	2 (8.70)	4 (18.18)	6 (37.50)
Presacral vertebrae, Greater than 26	22 (10.28)	31 (16.76)	22 (11.40)	30 (22.06)
	10 (41.67)	13 (56.52)	11 (50.00)	12 (75.00)

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LEGEND

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Upper row denotes number of affected fetuses (%) and lower row the number of affected litters (%)

Trend and pairwise significance levels are determined using one-sided tests.

Statistical analysis for fetal data including litter effects were performed by using a Rao-Scott modification to the Cochran-Armitage test where the Doe ID was the random effect for both trend and pairwise analysis.

# Statistically significant at  $P \leq 0.05$  (litter based analysis)

## Statistically significant at  $P \leq 0.01$  (litter based 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

Over-maceration during skeletal processing occurred in all groups: control group 47 fetuses[F] (5 litters[L]); limited to phalanges (22F, 3L); with fore/hind limbs (22F, 3L); and included portions of the axial skeleton (7F, 2L); 62.5 mg/kg dose group observed in 2F/2L; limited the phalanges in 1F, and included the fore/hind limbs in 1F; 125 mg/kg dose group (51F, 4L); limited the phalanges (13F, 2L); included fore/hind limbs (21F, 4L) and portions of the axial skeleton (3F, 1L); in the 250 mg/kg dose group (10F, 1L); limited the phalanges in 1F and included the fore/hind limbs in 9F.

**\*\* END OF REPORT \*\***