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DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity - Rats. **GUIDELINE No.:** 152-23
DP BARCODE: D225072 **SUBMISSION:** S503609

PC CODE: 217500 **TOX.CHEM.No:** 637C

TEST MATERIAL: Pelargonic acid **MRID No.** 43843508

CITATION: Wakefield, A.E. *"Teratology Screen in Rats"*. Hazleton Washington, Inc. Vienna, VA. Study ID: HWA 2689-101. 4/22/94. **MRID No. 43843508.** Unpublished.

EXECUTIVE SUMMARY: In a developmental toxicity study, pregnant CD rats (22/dose) were administered, by oral intubation, pelargonic acid in corn oil at 0 or 1500 mg/kg/day during days 6 through 15 of gestation. Treatment had no adverse effect on clinical signs, body weights, body weight gain, or food/water consumption. Pelargonic acid did not cause any fetal toxicity; the mean numbers of viable fetuses, early or late resorptions, implantation sites, corpora lutea, pre- and post-implantation losses, sex ratios and fetal body weights in the treated group were comparable to those of the control group. No developmental toxicity was seen; pelargonic acid did not increase the external, visceral, or skeletal malformations/variations in any of the fetuses. **The NOEL for maternal and developmental toxicity was 1500 mg/kg/day (Higher than the Limit-Dose) and the LOEL was >1500 mg/kg/day.**

This study is classified as **acceptable** and satisfies the Guideline requirement (§152-23) for a developmental toxicity study in rats.

I. INTRODUCTION

The objective of this study was to assess the effects of pelargonic acid on the embryonic and fetal development following oral administration to rats during the period of organogenesis.

II. MATERIALS AND METHODS

1. Test and Control Materials Pelargonic acid

Identification:	C-182
Purity:	100% (assumed)
Batch/Lot No.:	Not reported
Description:	Clear colorless liquid
Vehicle:	Duke's corn oil; Lot No. 80235

2. Test Animals — Female rats

Strain:	Crl:COBS CD (SD) BR, Charles River, NY
Age:	Approximately 14 weeks at Gestation
Weight:	199 - 292 g on Gestation Day 0
Identification:	Ear tags.
Acclimation:	Approximately 9 weeks.
Housing:	Individually in stainless steel cages
Food:	Purina Rodent Laboratory Chow ad libitum.
Water:	Tap water ad libitum
Environment:	Temperature, 70-82°F; Humidity, 20-70%; Light cycle, 12 hour light/12 hour/dark photoperiod
Group Assignment:	22 pregnant females randomly assigned to 1 vehicle control group and 1 treatment group.

3. Mating

Two females were paired with one male. Vaginal smears were taken daily during cohabitation, and the presence of a copulatory plug or sperm in the vaginal smear was considered evidence of mating. The day this evidence was seen was designated as Day 0 of gestation, and the female was then removed from the male's cage and housed individually.

4. Preparation of Dosing Solutions

A specific amount of test article was weighed into a pre-calibrated graduated beaker filled to a volume with appropriate amount of the vehicle [corn oil] and the mixture was kept homogenous by stirring on a magnetic stirrer during dosing. Dosing solutions were prepared fresh weekly and stored at room temperature between use.

5. Analysis of the Dosing Solutions

Stability and concentration analyses of the dosing solutions were not assessed during the conduct of the study in 1982. Therefore, on February 7, 1994, one formulation of pelargonic acid in corn oil (300 mg/ml) was prepared in the same manner as the original dosing solution and evaluated for concentration and 7-day stability.

Results: Concentration analyses indicated the formulation to be within 10% of target (Day 0 and Day 7 and the solution was stable at room temperature for 7 days.

6. Administration of Test Article

The vehicle and the test article were administered daily orally via gavage at a dose of 1500 mg/kg/day during days 6 through 15 of gestation. All groups received a dosing volume of 5 mL/kg body weight and the dose volumes were based on the most recent body weights except for the Day 15 dose which was actually based on the Day 12 body weight.

7. Observations

Animals were observed twice daily for mortality/moribundity and daily for clinical signs of toxicity. Body weights were obtained on Days 0, 6, 9, 12, 15, and 20 of gestation. Food and water consumption were measured during Days 6-9, 9-12, 12-15, 15-18, and 18-20 of gestation.

8. Termination

All surviving dams were sacrificed on gestation day 20. Gross pathologic alterations were recorded and the gravid uterus was weighed.

9. Cesarean Section

The thoracic, abdominal and pelvic cavities were examined for gross lesions (gross lesions were preserved in neutral buffered 10% formalin). The uterus was removed from the body, examined externally, weighed and then opened for internal examination. The following uterine parameters were examined/recorded: corpora lutea, number/placement of implantation sites, early/late resorptions, and live/dead fetuses.

10. Fetal Examinations

Each fetus was removed from the uterus and individually weighed and observed for gross external alterations. Approximately one-third of all fetuses from each litter was selected and processed for visceral examination by the Wilson Technique for soft-tissue alterations. The remaining fetuses were opened by longitudinal incision and the viscera were examined grossly; these fetuses were then eviscerated, stained with Alizarin red-S, and examined for skeletal alterations.

11. Statistical Analysis

One-way ANOVA was used to analyze maternal body weights, body weight gains, food and water consumption data, cesarean section, and fetal data.

12. Regulatory Compliances

This study was NOT CONDUCTED IN COMPLIANCE under GLP guidelines.

III. RESULTS

1. Maternal Toxicity

a. Survival

No mortality, abortions, or premature deaths occurred during the study.

b. Clinical Signs

No treatment-related clinical signs of toxicity were seen.

c. Body Weight Changes

No adverse effects were seen in body weight parameters. Mean body weight gains are presented below:

Dose mg/kg/day	Mean Body weigh Gain [G]						
	Days 0-6	Days 6-9	Days 9-12	Days 12-15	Days 6-15 (Dosing period)	Days 15-20 (Post-dosing)	Days 0-20 (Entire study)
0	20	5	9	11	25	60	105
1500	14	8	8	12	28	58	100

d. Food and Water Consumption

Mean food and water consumption values of the treated group were similar to that of the vehicle control.

e. Macroscopical Examination

No treatment-related macroscopical changes were observed in the dams sacrificed at termination.

2. Developmental Toxicity

Reproduction/fetal data are presented in Table 1. No biologically or statistically significant effects were seen on pregnancy rate, number of corpora lutea, number of implantations, total live fetuses per litter, resorption rate, number and percent of litters with resorption, fetal sex ratio, or fetal body weights.

Fetal external, visceral and skeletal variations are presented in Table 2. Fetal external and visceral malformations are presented in Table 3; no skeletal malformations were seen. No treatment-related or statistically significant external, visceral or skeletal variations or malformations were seen in any of the fetuses.

IV. DISCUSSION

In pregnant rats given oral administration of pelargonic acid at 0 or 1500 mg/kg/day during days 6 through 15 of gestation there were no mortality, abortions, or premature deliveries. Treatment had no adverse effect on clinical signs, body weights, body weight gain, or food/water consumption. Pelargonic acid did not cause any fetal toxicity; the mean numbers of viable fetuses, early or late resorptions, implantation sites, corpora lutea, pre- and post-implantation losses, sex ratios and fetal body weights in the treated group were comparable to those of the control group. No developmental toxicity was seen; pelargonic

acid did not increase the external, visceral, or skeletal malformations or variations in any of the fetuses. There were no distinct differences in the types or frequency of the findings seen between the control and treated group.

V. CONCLUSION

Pelargonic acid was not shown to be either a maternal or a developmental toxin at a dose of 1500 mg/kg/day. Under the conditions of this study, the NOEL for maternal and developmental toxicity was 1500 mg/kg/day (Higher than the Limit-Dose) and the LOEL was >1500 mg/kg/day.

Table 1. Cesarean Section Observations

Observations	Dose Level [mg/kg/day]	
[Mean ± S.D]	0	1500
No. Assigned	22	22
Females Gravid	22	20
Maternal Wastage		
# Died	0	0
# Sacrificed	0	0
# Aborted	0	0
# Early delivery	0	0
# Non pregnant	0	0
Total Corpora Lutea	349	295
Corpora Lutea/Dam	16 ± 2	15 ± 3
Total Implantations	298	253
Implantation/Dam	14 ± 2	13 ± 2
Total Live Fetuses	272	243
Live Fetuses/Litter	12 ± 3	12 ± 3
Total Resorptions	26	10
Early	26	10
Late	0	0
Resorption/Dam	1.2 ± 1.4	0.5 ± 0.8
Dead Fetuses	0	0
Pre Implantation Loss [%]	14.3 ± 9.2	13.0 ± 11.4
Post Implantation Loss [%]	9.2 ± 11.2	4.6 ± 8.1
Gravid Uterus Weight [g]	69 ± 14	67 ± 15
Sex Ratio ♂ / ♀	53/47	52/48

Crown-Rump length (cm) Males Females	3.76 ± 0.13 3.80 3.71	3.67 ± 0.27 3.74 3.60
Fetal Weight [g]	3.50 ± 0.21	3.44 ± 0.45

Data obtained from Study Report pages: 44-46, 48

Table 2. Summary of Fetal External, Visceral and Skeletal VARIATIONS.

	Fetuses		Litters	
Dose Level [mg/kg/day]	0	1500	0	1500
No. Examined Externally	272	243	22	20
Small fetus	1	0	1	0
Hydroureter(s)	1	1	1	1
Undulated ureter(s)	2	1	2	1
Dilated ureter(s)	16	10	8	7
Hindlimb appears oddly positioned	0	1	0	1
Total External Variation	20 7.4%	12 4.9%	11 50%	9 45%
No. Examined Viscerally	81	73	22	20
Small fetus	0	2	0	1
Increased renal pelvic cavitation	2	2	0	0
Total Visceral Variation	2 2.5%	2 9.1%	2 2.7%	1 5.0%
Number Examined Skeletally	191	170	22	20
Incomplete ossification of skull	26	29	10	13
Incomplete/nonossified hyoid body	25	24	9	9
Supraoccipital nonfused	0	1	0	1
Incomplete/unossified thoracic centrum	32	18	16	10
Bipartite thoracic centrum	11	11	8	6
Less than three caudal vertebrae ossified	0	4	0	2
Thoracic centrum missing	0	3	0	1
Lumbar centrum missing	0	3	0	1
Sacral arches and centra unossified	0	3	0	1
Sternebra(e) bipartite	1	0	1	0
Less than three sternebrae ossified	0	4	0	1
Wavy/bent ribs	2	3	2	1
13th rudimentary rib(s)	1	0	1	0
14th rudimentary rib(s)	1	2	1	2
Unossiifed pubis	1	4	1	2
Unossified ischium	0	3	0	1
Incomplete ossification of pubis	0	1	0	1
Total Skeletal Variations	73 38%	66 39%	19 86%	18 90%

Data obtained from Study Report pages: 50-51; 55; 59-62

Table 3. Summary of Fetal External, Visceral and Skeletal MALFORMATIONS.

	Fetuses		Litters	
Dose Level [mg/kg/day]	0	1500	0	1500
No. Examined Externally	272	243	22	20
Situs inversus	1	0	1	0
Cleft palate	0	4	0	1
Umbilical hernia	1	0	1	0
Total External Malformations	2 0.7%	4 1.6%	2 9.1%	1 5%
No. Examined Viscerally	81	73	22	20
Cleft palate	0	2	0	1
Total Visceral Malformations	0	0	2 2.7%	1 5.0%
Number Examined Skeletally	191	170	22	20
Total Skeletal Malformations	0	0	0	0

Data obtained from Study Report pages 53 & 57.

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