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Attention: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Constitution Avenue, N.W.
Washington, DC 20460-0001

Con

8EHQ-0605-16083

CBI

Re: TSCA 8(e) Submission of Benzoic Acid, 2-Hydroxy-, Mono-C14-15 Alkyl Derivatives, Calcium Salts Oral Gavage Reproductive/Developmental Toxicity Screening Study with Rats: Draft Report

Dear Sir or Madam:

The Lubrizol Corporation (Lubrizol) is submitting the draft final report on the oral gavage reproductive/developmental toxicity screening study with rats with benzoic acid, 2-hydroxy-, mono-C14-15 alkyl derivatives, calcium salts (CAS# 114959-46-5) pursuant to Section 8(e) of the Toxic Substance Act (TSCA). This study is being sponsored under the auspices of the American Chemistry Counsil's Petroleum Additives Panel Health Environmental Regulatory Task Group HPV Testing Consortium.

Statistically significant reductions in a number of reproductive and developmental parameters were observed in the study with benzoic acid, 2-hydroxy-, mono-C14-15 alkyl derivatives, calcium salts.

Lubrizol has not determined that these findings pose a significant risk of reproductive or developmental effects in humans. However, Lubrizol is submitting this information because it may be information that EPA considers to be reportable under TSCA 8(e).

The final report will be submitted to EPA when it is available.

None of the information in this submission is claimed as confidential business information.

If you have any questions, please contact Dr. Robert K. Hinderer at 216-447-5181 or robert.hinderer@noveon.com.

Sincerely,

Al Brightwell

8EHQ-05-16083

Al Brightwell
Vice President Environmental, Health, Safety & Product Regulatory Compliance

CC: Robert K. Hinderer, Ph.D.
Sarah Loftus McLallen, MSPH (ACC)

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CALVERT
LABORATORIES, INC.

Draft Report #1

TITLE: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test

Calvert Study No.: 0325RI38.001

Testing Facility: Calvert Laboratories, Inc.
Scott Technology Park
100 Discovery Drive
Olyphant, PA 18447

Study Sponsor: American Chemistry Council
Petroleum Additives Panel
Health Environmental and Regulatory Task Group
1300 Wilson Boulevard
Arlington, VA 22209

Date: 22 April 2005

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V. Summary

A. Title

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test

B. Objective

The purpose of this study was to evaluate the potential toxicity of a calcium alkyl salicylate on male and female reproductive performance such as gonadal function, mating behavior, conception, development of the fetus, parturition, and growth and development of the F_1 offspring from conception to Day 4 post-partum.

C. Methods

The test article, calcium alkyl salicylate, was supplied by Chevron Texaco as a brown viscous liquid. The test article was then prepared into dosing solutions for oral administration via gavage. One hundred experimentally naïve Sprague Dawley rats (50 males and 50 females), approximately 13-14 weeks old and weighing 329-418 grams for males and 239-296 grams for females at the outset of the study were assigned to treatment groups as shown in the tables below.

Group	Dose Level (mg/kg/day)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Animals	
				Male	Female
1. Control (vehicle)	0	0	10.0	15	15
2. Low-dose	160	16	10.0	10	10
3. Mid-dose	400	40	10.0	10	10
4. High-dose	1000	100	10.0	15	15

Estrous cycle evaluation was performed daily for 2 weeks prior to treatment initiation and daily during the treatment and cohabitation periods. Male animals were dosed once daily for a minimum of 2 weeks prior to cohabitation, during cohabitation and until scheduled sacrifice for a minimum of 28 days. Female animals were dosed once daily for a minimum of 2 weeks prior to cohabitation, during cohabitation and from presumed

Gestation Day 0 through Post-partum Day 4 inclusive (approximately 54 days). Five animals/sex/group in Groups 1 and 4 were not mated. Following the treatment period, these animals remained on test, untreated for a 14-day recovery period. Mortality and clinical observations were evaluated daily. Body weights for the F_0 generation males were recorded weekly beginning on the first day of dosing. Body weights for the F_0 generation females were recorded weekly beginning on the first day of dosing and on presumed Gestation Days 0, 7, 14, 17 and 20 and on Days 0 and 4 post-partum. Body weights for the F_1 generation males and females were recorded within 24 hours of parturition and on Day 4. Food consumption was recorded once weekly for the F_0 generation males until initiation of cohabitation and for the F_0 generation females intervals 0-6, 6-12, 12-17 and 17-20 of gestation and 0-4 post-partum. Blood for evaluation of hematology, coagulation and clinical chemistry was collected from 5 randomly selected animals/sex/group prior to terminal sacrifice. F_0 generation females showing no evidence of mating were sacrificed 24-26 days after the last day of the mating period. All surviving F_0 generation females were sacrificed Day 5 post-partum. All surviving F_0 generation males were sacrificed within two weeks after the end of the mating period. Selected tissues were harvested at necropsy, selected organs weighed, and selected tissues from the control and high dose groups evaluated microscopically for all surviving F_0 generation animals. All F_1 generation animals were sacrificed on Day 5 post-partum and a gross necropsy was performed.

D. Results and Conclusions

There was no test article-related mortality on this study.

There were no clinical signs of toxicity noted during the study which were considered to be related to treatment with the test article. Noisy respiration was noted throughout the study in all dose groups which was considered related to the consistency of the test article and inhalation during the gavage procedure.

There were no definitive test article-related clinical observations for neonates noted.

Males dosed at 1000 mg/kg had a statistically significantly reduced mean weight gain on Day 8 compared to controls. This resulted in a statistically significantly reduced group mean body weight for the 1000 mg/kg dose group males on Day 8. During the second week of the study, the group mean body weight gain was statistically significantly increased for the 1000 mg/kg dose group males compared to controls. This resulted in the group mean body weights for the high dose males becoming comparable to controls by Day 15. A slight, yet statistically significant, increase in group mean body weight gain was also noted in the 1000 mg/kg females at Day 15 but there were no test article-related changes in group mean body weights for the females at any timepoint.

Group mean dam body weights were statistically significantly reduced for the 1000 mg/kg dose group on Days 7-14 and 14-17 of gestation as compared to controls. During lactation, there were no test article-related changes in group mean dam body weight or body weight gain.

There were no test article-related changes in group mean pup body weight on Day 0 or Day 4. However, total litter weight was reduced for the 1000 mg/kg dose group.

There was a statisically significantly reduced group mean food consumption for the 1000 mg/kg males on Day 8. There was a statistically significantly increased group mean food consumption for the 1000 mg/kg females on Day 15. Group mean food consumption was increased for the high dose males and females at various times during the end of the treatment period and the recovery period. During gestation and lactation there were no definitive test article-related changes in dam food consumption.

The copulatory index and fertility index were reduced for the 1000 mg/kg dose group. The number of dams with live young born was reduced for the 1000 mg/kg dose group. The total number of neonates was reduced both at Day 0 and at Day 4 for the 1000 mg/kg dose group compared to controls. There was no test article-related difference in post-natal loss, although there did appear to be an increase in pre-natal loss for the 1000 mg/kg dose group.

There were no test article-related changes in sensory reactivity to auditory, visual and proprioceptive stimuli, grip strength or motor activity.

There were no test article-related changes in hematology or coagulation parameters.

Alkaline phosphatase was increased for males dosed at 400 mg/kg and males and females dosed at 1000 mg/kg. Alanine aminotransferase was increased for males dosed at 1000 mg/kg. Total protein was decreased for males dosed at 1000 mg/kg. Albumin was decreased for males dosed at 400 and 1000 mg/kg. Triglycerides were increased for males dosed at 1000 mg/kg. By the end of the recovery period, all values were comparable to controls or within normal historical control values.

There were no test article-related gross necropsy findings.

Liver weight (absolute, relative to body weight ratio and relative to brain weight ratio) was increased for males and females (gravid and non-gravid) dosed at 400 and 1000 mg/kg. An increase in adrenal weight was noted for the 1000 mg/kg females (absolute and relative to brain weight ratio for gravid animals and relative to body weight ratio for non-gravid animals). Liver and adrenal weights were comparable to controls at the end of the recovery period.

Test article related findings indicative of an irritant effect on the nonglandular region of the stomach were observed in Group 4 rats of both sexes and were more prominent in females. These findings included epithelial hyperplasia, acute inflammation, erosion, and ulceration. In Group 4 males, minimal to mild epithelial hyperplasia was observed in three rats accompanied by minimal acute submucosal inflammation in one of them. These changes were not observed in vehicle control males. In addition, one Group 4 male found dead had moderate ulceration and epithelial hyperplasia of the nonglandular region. In Group 4 females, moderate epithelial hyperplasia with mild to moderate acute inflammation in the submucosa was observed in three rats accompanied by acute inflammation within the epithelium, erosion or ulceration. An additional rat had mild epithelial hyperplasia only. Although minimal epithelial hyperplasia and acute submucosal inflammation were observed in two vehicle control females receiving corn oil alone, the changes

observed in rats receiving calcium alkyl salicylate were more severe, especially in females. A NOEL for this effect could not be determined as the lower doses were not examined.

In conclusion, administration of a calcium alkyl salicylate at 1000 mg/kg/day once daily for a minimum of 28 days (males) or approximately 54 days (females) resulted in general toxicity including initial reductions in body weight gains and body weights for males followed by increased body weight gains for males and females, an increase in liver enzymes and liver weight (also noted for the 400 mg/kg males and females), increased adrenal weights for females, and hyperplasia and inflammation of the nonglandular region of the stomach (an effect which was not examined in the lower dose groups). Reproductive changes for the 1000 mg/kg dose group included reduced copulatory and fertility index, gestation weight, number of dams with live young and number of neonates. Based on these findings, the NOEL (No-Observed Effect Level) is considered to be 160 mg/kg.

DRAFT