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Pebulate

Supplement to DER, MRID 40970001 - Reproduction study in rats
This supplement provides an executive summary to upgrade the original DER

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AMENDED DATA EVALUATION RECORD

STUDY TYPE: Reproduction study
DP BARCODE: D183690
PC CODE: 041403 CASE No: 1114-71-2
CASWELL No.: 710
TEST MATERIAL (PURITY): Pebulate (97.3%)
SYNONYMS: Tillam
SPONSOR: ICI Americas, Inc.
CITATION: Keller, K.A. (1988) Two Generation Reproduction/Fertility Study in Rats (T-12922). International research and Development Corporation, MI. Study No. 153-196. October 19, 1988. MRID 40970001. Unpublished.

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 40970001), pebulate technical (97.3% a.i.) was administered in the diet to Charles River COBS CD rats at dose levels of 0, 15, 120 or 1000 ppm (approximately 0, 0.8, 6, or 50 mg/kg/day by a standard conversion factor). Exposure to F_0 parental groups (26/sex/group) began at 8 weeks of age and lasted for 56 days prior to mating. The selected F_{1b} pups began receiving the test diets at 4 weeks of age and continued on them for a minimum of 98 days prior to mating. Because of high mortality among the 1000 ppm F_0 males, only 21 males and 26 females from that group were paired for the F_{1a} mating, 17 males and 25 females were paired for the F_{1b} mating, and the F_1 1000 ppm group was not mated to produce the F_{2a} or F_{2b} litters.

High mortality was observed in the high-dose F_0 (34.6% and 3.8%) and F_1 (93.3% and 38.7%,) for males and females, respectively. The most notable clinical signs occurred in the high-dose rats included moribundity, convulsions, loss of righting reflex, labored breathing, dilation of eyes, coldness when touched, thin or emaciated appearance, low carriage, ataxia, paleness of exposed skin areas and eyes, and blue discoloration (focal and generalized). Mean body weight gains were decreased in the 120 ppm F_0 males (↓ 4-8%) and F_1 males (↓ 5-8%) and females (↓ 6-18%) and in the 1000 ppm F_0 (↓ 7-13% and ↓ 6-12%) and F_1 (↓ 19-36% and ↓ 11-26%) for males and females, respectively. Mean weekly food consumption for the mid- and high-dose F_0 males and F_1 males and females were lower than the control (5-19% and 10-33%, respectively) throughout most of the study. Decreased hemoglobin concentration (↓ 9.8% and ↓ 16.8%) and hematocrit (↓ 4.9% and ↓ 3.6%) and increased platelet counts (↑18.9% and ↑16.3%) were observed in females only at the mid- and high-dose, respectively. Necropsy revealed treatment-related

1

hemorrhages in a number of different organs in animals from the 1000 ppm group that died or were sacrificed in extremis. In addition, unclotted or severely clotted blood in cranial, thoracic and abdominal cavities and in heart were observed in 1000 ppm males. Nothing remarkable was observed in the low- and mid-dose groups.

Reproductive parameters which measured spermatogenesis, estrous cycle, gestation length, copulatory and fertility indices did not show treatment-related abnormalities. However, fertility in the F_1 males and females was low in both the control and treated groups in comparison to their F_0 parents.

Litter sizes and gestation survival index were similar in the control and treated groups, in the F_{1a}, F_{1b}, F_{2a}, and F_{2b} generations (high-dose F_1 rats were not mated). Pup survival between lactation days 0-21 was similar in the control and treated groups. Increased pup mortality (52.9%) was observed in the high-dose group between lactation days 16 and 24. Mean pup body weights at birth for the treated groups were comparable with the control values in all of the generations (F_{1a}, F_{1b}, F_{2a}, F_{2b}). Decreased pup weights (↓6.3-21.7%) in the high-dose F_{1a} and F_{1b} groups were noted on lactation days 7, 14, and 21. Necropsy of pups /weanlings sacrificed on lactation day 4 or 21 did not show treatment-related effects. However, 61% of the high-dose males and 57.1% of the high-dose female weanlings, sacrificed at day 24, had localized or generalized subcutaneous hemorrhages; head, neck, and limb areas were regions most often affected.

The parental NOAEL is 15 ppm (approximately 0.8 mg/kg/day) and the LOAEL is 120 ppm (approximately 6 mg/kg/day) based on decreased weight gain and food consumption in both sexes; decreased hemoglobin, hematocrit, and increased platelet count in females. **The off-spring NOAEL is 120 ppm (approximately 6 mg/kg/day) and the LOAEL is 1000 ppm (approximately 50 mg/kg/day)** based on decreased pup survival between 16 and 24 days of age, decreased pup growth during lactation days 7-21, and subcutaneous hemorrhages in males and females. **The Reproductive NOAEL is 1000 ppm (approximately 50 mg/kg/day) (HDT).**

This study is clasified **Unacceptable (Guideline).** This study does not meet guideline requirements for a 2-Generation Reproduction Study because only two doses of pebulate were used in the F_1 generation and only 10, 14, and 17 litters were available for examination in the F_1 control, low-dose and mid-dose groups, respectively. In addition, low fertility was observed in the control. However, little additional information, if any, would probably be obtained about the reproductive/developmental effects of pebulate by repeating this study.

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