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Pebulate

Supplement to DER, MRID 41213001 - Combined Chronic Toxicity/Carcinogenicity in rats
This supplement provides an executive summary to upgrade the original DER

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AMENDED DATA EVALUATION RECORD

STUDY TYPE: Chronic Feeding/Carcinogenicity study
DP BARCODE: D183690
PC CODE: 041403 CAS No: 1114-71-2
CASWELL No.: 710
TEST MATERIAL (PURITY): Pebulate (97.3%)
SYNONYMS: Tillam
SPONSOR: ICI Americas, Inc.
CITATION: Daly, I.W. (1989) A Two-Year Chronic Toxicity/Oncogenicity Study of Tillam Technical in Rats. Bio/Dynamics, Inc. East Millstone, NJ Study No. 86-3036. May 11, 1989. MRID 41213001. Unpublished.

EXECUTIVE SUMMARY: In a 2-year feeding/carcinogenicity study (MRID 41213001), pebulate technical (97.3% a.i.) was administered in the diet to Charles River rats (60 or 70/sex/group) at dose levels of 0, 15, 150, or 1500 ppm (equivalent to 0, 0.74, 7.12, or 75.6 mg/kg/day for males and 0, 0.85, 9.4, or 99.44 mg/kg/day for females, respectively) for two years.

Increased mortality was observed in the high-dose males only during the first 7 months of the study. Clinical signs (pale eyes and extremities, red oral and nasal discharges and general poor condition) were observed in the high-dose males which died or were sacrificed moribund during the first year of the study. Ophthalmological findings (zonal disjunction, retinal degeneration and cataracts) were observed mostly in the high-dose males and females, and less frequently in the mid-dose males and females. Decreased body weights in the high-dose males (↓7-21.4%) and females (↓6.4-39.9%) throughout the study (weeks 2-105), and in the mid-dose males (↓3.4-8.2%) during weeks 3-69 and the mid-dose females (↓4.2-16.6%) during weeks 3-97. Significant body weight gain deficits were observed in the high-dose group (↓39% in males and ↓56.2% in females) when compared to the control. Increased food consumption was observed in the high-dose males and females; and occasionally for the mid-dose males and females. Hematology parameters showed an increased thromboplastin times in the high-dose males and females and increased Factor VII values in the high-dose males at the 12 and 24 months sampling intervals. Clinical chemistry showed increased blood cholesterol and BUN levels and decreased triglyceride and glucose values in the high-dose males and females at most sampling times. Necropsy did not reveal treatment-related abnormalities when compared with controls. No significant difference in organ weight was observed in the low- and mid-dose males and females compared to the controls.

In the high-dose group, most organ weights and organ/body weight ratios were statistically different from those of the control group. However, since these differences from control were secondary to the observed decreases in body weight gain, they were not indicative of primary organ toxicity. Increased incidence and severity of necrotic lesions in the livers of the high-dose male rats dying prematuring. Other microscopic findings in the high-dose male rats dying prematurely included hemorrhages in the epididymides, liver, testes, thoracic spinal cord and thymus; inflammation of epididymides and skin; islet hyperplasia (pancreas) and extramedullary hematopoiesis (liver). Although pebulate is structurally related to compounds which are capable of causing Wallerian-type degeneration in brain, spinal cord and peripheral nerves, this was not observed in this study.

There was no evidence of carcinogenic potential for pebulate in this study. The highest level of pebulate tested, 1500 ppm, was a maximum tolerated dose (MTD) for both sexes.

The NOAEL is 15 ppm (equivalent to 0.74 mg/kg/day for males and 0.85 mg/kg/day for females) and the LOAEL is 150 ppm (equivalent 7.12 mg/kg/day for males and 9.4 mg/kg/day for females) based on decreased body weights of both sexes and increased incidence of cataracts in both sexes.

This study is classified **Acceptable/Guideline** and satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity study in rats.

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