Pebulate

4/13/1995

Supplement to DER, MRID 40969701 - One-Year Toxicity Study in Dogs
This supplement provides an executive summary to upgrade the original DER

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AMENDED DATA EVALUATION RECORD

STUDY TYPE: One-year dog study
DP BARCODE: N/A
PC CODE: 041403
CASWELL No.: 710
TEST MATERIAL (PURITY): Pebulate (97.3%)
SYNONYMS: Tillam
SPONSOR: Stauffer Chemical Company
CITATION: Pettersen, J.C. and Taylor, D.O.N. (1988) One-year Toxicity Study with Tillamin Beagle Dogs. ICI Americas Inc. Study No. T-13000. December 9, 1988. MRID 40969701. Unpublished.

EXECUTIVE SUMMARY: In a one-year study (MRID 40979701), pebulate technical (97.3% a.i.) was administered to beagle dogs (4/sex/group) via gelatin capsules for 12 months at dose levels of 0, 5, 25, 50, or 100 mg/kg/day.

Treatment-related clinical signs included increased incidence of emesis, blood and/or mucous in feces in the 25 mg/kg/day and above males and females. Abnormal behavior was observed in one low-dose male (nonsurvivor) and all high dose males. Neurological abnormalities were observed in 3 males, one in each of the low-, mid-, and high-dose groups. Decreased total body weight gain were observed in males at 50 and 100 mg/kg/day groups (↓51.5% and 48.5%, respectively). Food consumption was comparable among control and treated groups. Hematology parameters showed significant decreases in RBC count, hemoglobin concentration and hematocrit in males at 25 mg/kg/day and above and in females at 50 and 100 mg/kg/day. Other findings included significant increases of total leukocyte count in the 100 mg/kg/day females and platelet count in the 50 and 100 mg/kg/day groups of both sexes. Brain cholinesterase (ChE) activity was not inhibited at any dose level in both sexes. RBC ChE activity was not inhibited in the females at all dose levels and only sporadic inhibitions occurred in males. Significant inhibition of serum ChE activity was observed at month 1 in the 25, 50, and 100 mg/kg/day male groups. Increased absolute and relative liver weights were observed in both sexes at 25 mg/kg/day and above. Moderately severe Wallerian-type degenerative changes in the spine cord and peripheral nerves were observed in the 100 mg/kg/day males and females. Other remarkable histopathological findings included an increased cellularity of bone marrow in the 50 and 100 mg/kg/day males and females; increased lipofuscin deposition in kidney at 50 and 100 mg/kg/day and hemosiderin deposition in the liver

and spleen, mostly in the 25 mg/kg/day and above males and females.

The NOAEL for males is <5 mg/kg/day (LDT) based on abnormal behavior, ataxia, severe convulsions, and congestion in both kidneys in one dog sacrificed on day 316. **The NOAEL for females is 5 mg/kg/day and the LOAEL is 25 mg/kg/day** based on blood in feces, increased absolute and relative liver weight, and increase in severity of lipofuscin deposition in kidneys and hemosiderin deposition in liver and spleen.

This study is classified **Acceptable (Guideline)** and satisfies guideline requirement for an one-year dog study (83-1).

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