

January 23, 1997

**MEMORANDUM**

**SUBJECT:** Pebulate (Tillam): Review of Subchronic Neurotoxicity Study (82-7)

Rereg. Case No. 2500  
CAS Reg. No. 1114-71-2

Chemical Code No. 041403  
Tox. Chem. No. 710

Sponsor: ZENECA Inc., Agricultural Products, Wilmington, DE.

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**TO:** Virginia Dietrich/Ron Kendall, PM Team 51  
Accelerated Reregistration Branch  
Special Review and Reregistration Division (7508W)

Toxicology Branch I/HED has completed an evaluation of the following study:

Guideline No.	MRID No.	DP Barcode No.	Acceptability
82-7	43231001	D204011	Yes

In this study, Pebulate (purity: 96%) was administered in the diet to groups of 12 male and 12 female Wistar-derived rats for 13 weeks. The nominal doses used were 0, 50, 250 or 1000 ppm. The actual doses received (mg/kg of body weight/day) were: 0, 3.9, 19.4 or 78.2 (males) and 0, 4.5, 21.5 or 85.2 (females). In previous feeding studies with Pebulate, doses > 1000 ppm caused excessive mortality in the male rats.

The only treatment-related finding observed in this study was the

statistically significant inhibition of brain cholinesterase (ChE) activity in the 250 ppm male group (8.1%) and in the 1000 ppm male and female groups (13.2% and 22.5%, respectively). A minimal sciatic nerve fiber degeneration, observed in the 1000 ppm males (2/6 or 33% vs. 1/6 or 17% in the controls) and females (2/6 vs. 1/6 in the controls) might also be treatment-related (other groups were not examined). There was no mortality in the current study.

Relative to the control values, decreases in food consumption (7-16%) and the resulting decreases in body weight (5-6%) were observed at varying time intervals in all male and female groups. However, these decreases, although statistically significant, were small and dose-unrelated, and therefore difficult to interpret. The testing facility attributed the decreases in food consumption to the palatability of Pebulate.

Based on the above findings, the LOEL and NOEL for neurotoxicity are 1000 ppm (mg/kg/day: 78.2 ♂ and 85.2 ♀) and 250 ppm (mg/kg/day: 19.4 ♂ and 21.5 ♀), respectively. The LOEL and NOEL for systemic toxicity (including the inhibition of brain ChE activity) are 250 ppm and 50 ppm (mg/kg/day: 3.9 ♂ and 4.5 ♀), respectively.

This study is classified as Acceptable and satisfies the guideline requirement for a subchronic neurotoxicity study in the rat (82-7).

This study was submitted as the 6(a)(2) data, but it was not stated why. Toxicology Branch I/HED cannot determine why this study is regarded by the registrant as the 6(a)(2) data.

Sign-off date: 04/17/97  
DP Barcode: D204011  
HED DOC Number: 012195  
Toxicology Branch: TB1

3