October 17, 1996

MEMORANDUM

SUBJECT: Pebulate (Tillam): Review of Acute Neurotoxicity Study (81-8) - Original and Revised (Addendum) Reports

Rereg. Case No. 2500 Chemical Code No. 041403
CAS Reg. No. 1114-71-2 Tox. Chem. No. 710

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

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TO: Kathleen Depukat/Paul Lewis, PM Team 51
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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
81-8	43217401 *	D203584	Yes
81-8	43965401 **	D225342	Yes

* Original submission.
** Original submission, revised by inclusion of negative clinical observations (as well as positive ones) and by submitting new histopathology findings for the brain tissue after re-reading of the slides.

In this study, Pebulate (purity: 96%) was administered in a

single gavage dose to groups of 10 male and 10 female Wistar-derived rats. The doses (0, 50, 150 or 500 mg/kg of body weight), corrected for purity, were administered in corn oil.

The following treatment-related findings were observed in the 500 mg/kg male and/or female groups: **(1)** Clinical findings (decreased activity, hunched posture, splayed gait, decreased visual placement response, piloerection, irregular breathing, ptosis, chromodacryorrhea, rigidity during handling, and signs of salivation and urinary incontinence; **(2)** Decreases in group mean body weight and food consumption during the first week after dosing; **(3)** Increases in the landing foot splay and time to tail flick; **(4)** Decreases in the hindlimb grip strength (males) and motor activity; and **(5)** Neuronal cell necrosis in the pyriform and dentate gyrus cortices of the brain. Clinical signs were observed at 5-6 hours after dosing and disappeared within 1-2 days.

Treatment-related effects, observed in the 150 mg/kg group, were: **(1)** Decreased activity, increased breathing rate and decreased motor activity in females; and **(2)** Increased incidence of neuronal cell necrosis in the brains of males and females (not observed after re-reading of the slides).

Treatment-related findings were not observed in the 50 mg/kg group. Pebulate had no effect on cholinesterase (ChE) activities in brain, plasma and erythrocytes, neuropathy target esterase (NTE) activity in brain, brain measurements (weight, length and width), and macroscopic pathology in this study.

Based on the above findings, the LOEL and NOEL for neurotoxicity are 150 mg/kg and 50 mg/kg, respectively. This study satisfies the guideline requirement for an acute neurotoxicity study in the rat (81-8).

Sign-off date:	02/11/97
DP Barcode:	D225342
HED DOC Number:	012159
Toxicology Branch:	TB1