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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

JUL 8 1991

February 7, 1991

MEMORANDUM

SUBJECT: Avermectin Semi-Synthetic (MK-244); Rationale for  
Selecting MTD for Rat and Mouse Carcinogenicity Studies

Caswell No.: 63AB  
Project No.: 1-0545  
ID No.: 281972  
Record No.: 5389053

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*William Dykstra*  
*2/7/91*

TO: Adam Heyward, PM Team #15  
Insecticide-Rodenticide Branch  
Registration Division (H7505C)

THRU: Roger Gardner, Section Head  
Review Section I, Tox Branch I, IRS  
Health Effects Division (H7509C)

*J. Gardner 06/10/91*  
*(for RG)*  
*1/26/24/91*

Requested Action: RD requests that Tox Branch I consider and comment on the rationale for the MTD's for the chronic rat and mouse studies proposed by Merck Company for a new semi-synthetic avermectin (MK-244).

Conclusions and Recommendations:

1. Although it is policy not to select dose levels for studies, Toxicology Branch does not object to the rationales for the MTD's selected for the rat and mouse carcinogenicity studies.

The selected doses for the rat study are 0.25, 1.0, and 5.0 mg/kg/day. These doses are essentially based on a 14-week study in which decreased body weight gain, deaths, ~~tumors~~, and CNS lesions were observed at 5.0 mg/kg/day or greater. ^ CNS lesions also were present at 2.5 mg/kg/day.

**TREMORS**

The selected doses for the mouse study are 0.5, 2.5, and 12.5 mg/kg/day. These doses are based on a 14-week study in which possible deaths, and decreased body weight gain were

observed at 15 mg/kg/day but not at 10.0 mg/kg/day, or lower. In light of the slightly reduced level at 12.5 mg/kg/day in comparison to the effects observed at 15 mg/kg/day, Toxicology Branch I does not object to rationale for selection of the MTD.

Review:

1. No new toxicology data were submitted. Attached is the Merck Company's memo describing the dose selection for the two rodent bioassays.

Attachments