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
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William Dykstra 2/7/91

TO: Adam Heyward, PM Team #15
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THRU: Roger Gardner, Section Head
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Health Effects Division (H7509C)

06/10/91 (for RG)
KB 6/24/91

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-synethic 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

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