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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Second Generation Semi-Synthetic Avermectin (MK-244); Status of Ongoing Mouse 93-Week Dietary Carcinogenicity Study TT #91-033-0: Response From Merck & Co.

Tox.Chem No.: 63AB
MRID No.: None
DP Barcode No.: D179905, D180831
Submission No.: S420499, S422185

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THRU: Roger Gardner, Section Head, Toxicologist
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ACTION REQUESTED: Merck & Co. is currently conducting a 93-week mouse dietary carcinogenicity study with semi-synthetic avermectin (MK-244). In two separate letters from Merck to Toxicology Branch (TB-I), dated June 18, 1992 and July 15, 1992, Merck summarizes the results of the ongoing study and details their plans to terminate the study at 78 weeks. TB-I has been requested to respond to the Merck letters.

CONCLUSIONS: TB-I recommends that dosing of the high-dose males continue, without interuption, up to the scheduled sacrifice at 78

weeks or until the survival of the high-dose male group reaches 30% (assuming this level of survival occurs before 78 weeks). If a 30% level of survival occurs before 78 weeks, the high-dose group should be sacrificed. The remaining treated male and female groups and the control groups should be sacrificed at the scheduled 78 weeks (terminal sacrifice). This detailed information was telephoned to Dr. L. Grosso of Merck, and the July 15, 1992 letter is an acknowledgement and agreement by Merck with the TB-I advice.

REVIEW: Merck reported on the highly significant decreases in body weight gain (approximately -65% and -50% of concurrent controls in high-dose males and females, respectively) and survival as of Drug Week 68 (survival in the high-dose male and female dose groups was 50% and 56% respectively, while that of the remaining groups in this study ranged from 76-90%). Merck presented summary data to explain their plans to discontinue dosing the high-dose males and females and terminate the study at 78 weeks, instead of 93 weeks, as originally planned. In telephone conversations with Merck, TB-I detailed their recommendations as stated in the "Conclusion" of this memo.