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

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JUN 28 1988

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: FMC Response to EPA Review of 52 Week Chronic Oral  
Toxicity Study in Dogs

TC: Mr. George LaRocca  
Product Manager 15

FROM: Byron T. Backus, Toxicologist  
Toxicology Branch, HED (TS-769C)

*Byron T. Backus*  
6/23/88

THROUGH: Marc'a van Gemert, Ph.D.  
Section Head, Review Section III  
Toxicology Branch, HED (TS-769C)

*M. van Gemert*  
6/21/88

and

Theodore M. Farber, Ph.D., D.A.B.T.  
Branch Chief  
Toxicology Branch, HED (TS-769C)

*W. Farber*

Project No. 8-0753

Tox. Chem. No. 463F

Action Requested:

FMC Corporation has submitted information supporting a revision of the NOEL for Bifenthrin from 0.75 mg/kg/day to 1.5 mg/kg/day in a 52 week chronic dog feeding study.

Background:

In a previous review (DER dated 2, 3/87) the Toxicology Branch classified a chronic (1 year) dog feeding study with Bifenthrin as core minimum data, with a NOEL of 0.75 mg/kg/day and a LEL of 1.5 mg/kg/day based on decreased creatinine phosphokinase (CK) at 52 weeks. FMC has now submitted material which includes historical control CK data from female dogs in other 52-week feeding studies, as well as references discussing the biological significance of CK.

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Comments and Recommendations:

1. After examining the FMC response, the Toxicology Branch recommends that the NOEL for this study be revised from 0.75 to 1.5 mg/kg/day, and that the LEL be revised from 1.5 to 3 mg/kg/day. Additionally, based on the historical control data provided by the performing laboratory, as well as literature references demonstrating considerable variability in this parameter and a lack of biological significance relating to low levels of creatinine phosphokinase (CK), the Toxicology Branch concurs with the position taken by FMC that no dose-related effect was observed in this parameter.
2. The test material was administered in gelatin capsules at 0, 0.75, 1.5, 3 and 4 mg/kg/day to groups of 4M, 4F beagles. The basis of the revised LEL is the intermittent tremors observed in 1/4 males and 2/4 females in the 3 mg/kg/day group between weeks 16 and 23 of the study. All dogs (4M, 4F) receiving 4 mg/kg/day showed tremors between weeks 15 and 29. Tremors were not observed in dogs receiving 0.75 or 1.5 mg/kg/day of the test material. A significantly elevated mean glucose in 1.5 mg/kg/day males at 52 weeks was not part of a dose-related trend (mean glucose in 3 mg/kg/day males was lower than that for 1.5 mg/kg/day males, and was not significantly elevated with respect to the control mean).
3. The Preliminary Acceptable Daily Intake (PADI) for Bifenthrin had been set at 0.0075 mg/kg/day, based on the previously set NOEL (0.75 mg/kg/day) in the chronic dog study and utilizing a 100-fold safety factor (refer to the memorandum from C. Frick to George LaRocca, April 16, 1987). It is now recommended that, on the basis of the revision of the NOEL to 1.5 mg/kg/day, the PADI be revised accordingly to 0.015 mg/kg/day. The systemic NOEL in a 2-year rat feeding/oncogenicity study was 50 ppm (2.5 mg/kg/day), so the basis of the PADI remains the NOEL from the dog study.

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