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PC 129121

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

Office of Prevention, Pesticides and Toxic Substances

May 3, 2000

MEMORANDUM

SUBJECT: Secondary Review of DER for Companion Animal Safety Study

DP Barcode: **D265179**
Submission: S572131
PC Code: 129121
MRID: 44942009

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer
Reregistration Branch I, Health Effects Division (7509C) Virginia A Dobozy 5/3/00

TO: John Redden, Branch Senior Scientist
Technical Review Branch, Registration Division (7505C)

Action Requested: Provide secondary review of DER for MRID 44942009

Recommendation: See the attached Memorandum from the Companion Animal Safety Committee

Memorandum of Companion Animal Safety Committee - May 3, 2000

The following DER prepared by the Technical Review Branch, RD, was reviewed by Drs. Kit Farwell and Virginia Dobozy.

DP Barcode: D265179

Product: Frontline Plus for Cats [fipronil and methoprene (PC Codes: 129121 and 105402, respectively)]

Study Title: Fipronil/s-Methoprene Topical Solution: Target Species Safety Study in the Cat

The following is the executive summary from the DER (MRID 44942009).

In a companion animal safety study, MRID 44942009, Fipronil/s-Methoprene solution for cats (Active Ingredients: Fipronil:10% w/v; (S)-methoprene:12% w/v) was topically applied at dose levels of 0.5 mL (1X), 1.5 mL (3X) or 2.5 mL (5X times the maximum recommended dose) to groups of 6 male and 6 female kittens, 52-59 days old on study Day 0. Applications were centered on the mid-point of the dorsal neck between the base of the skull and shoulder blades. Controls were not dosed. Animals were treated on Study Day 0 and again on Study Day 28. The report includes results of the study up to Day 42.

The animals were observed hourly for 6 hr following each treatment, and twice daily on every study day (with the exception of Day –14 when they were observed only once). Clinical evaluations were conducted on Days –14 (or –13), on the day of each treatment (Day 0 and Day 28) and on Study Days 1, 3, 7, 14, 21, 29, 31, 35 and 42. Body weights were recorded at the start of acclimation on Study Day-14 (with the exception of 5 cats who were weighed on Day-13), prior to dosing on Study Days 0 and 28, and on Study Days –7, -1, 7, 14, 21, 35, and 42. Blood samples were obtained from the jugular vein on Study Days-4, or –3 (depending on the set) and thereafter on Days 14, 28 (before treatment) and 43.

No clinical signs of erythema, edema, alopecia or abnormal hair coat condition were observed 1-6 hr post-dosing in any of the treated animals or during any of the other observation periods from Study Day –14 to Study Day 42. Animals in all treated groups (maximum of 9 of 12 in 5X group on Study Day 28) had skin flakes and off-white material at the application site, and four in the 5X group exhibited pruritus on Days 1, 2 or 3. No ocular, muscular, cardiovascular, or behavioral changes or abnormalities of the mucus membranes were observed in the treated cats. There were no morphological abnormalities in RBCs that could be attributed to treatment.

Overall, no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology, were reported. Although there were statistically-significant changes in hematology and clinical chemistry parameters in some treatment groups at some sampling times (i.e., reduction in mean corpuscular volume; reduction in % neutrophils, increase in % monocytes; increase in eosinophils, increase in reticulocytes, increase in urea), none of the changes followed a clear dose-response relationship and most were within the normal reference range.

Summary statistics were presented by sex for each treatment group only in those cases where a statisitically significant change was observed ($p < 0.10$). It is recommended that mean values of all hematological and clinical chemistry parameters for each sex for each treatment group and for all sampling periods, as well as individual data, be included in the final report. Because a full complement of animals was not available at the start of the study, the animals were tested in sets, and the data for each study day was collected on five separate dates (one for each set). The guidelines do not require that all the animals be treated and observed at the same time points. This interim report did not include the results of necropsies that were scheduled for Study Day 154.

This study deviated from the companion animal safety study Guidelines (OPPTS 870.7200), in that blood samples were not collected within 24 hours of treatment on Day 0 and Day 28. Therefore, the study is classified as Unacceptable. In order for this study to be upgraded, we would need to have hematology and clinical chemistry data demonstrating no effects at 24 hours following each application for at least 5X group relative to their controls. We could accept a short term (28-day study) in which the test material was applied on days 0 and 14. In addition, the Agency would need to have mean and individual values of all hematology and clinical chemistry parameters for each sex at each sampling period.

Conclusions of CAS Committee

Drs. Farwell and Dobozy disagreed with the RD study classification as unacceptable (on the basis that the blood samples were not collected within 24 hours of treatment on Days 0 and 28, as required by the Companion Animal Safety Study Guidelines). They thought the study should be classified as Acceptable for the following reasons: 1) the remainder of the study was conducted according to the Guidelines; 2) there was no evidence of toxicity in any of the animals; 3) as fipronil is registered at this concentration in other products, there are CAS studies with no evidence of toxicity at 5x. In addition, methoprene is used with many other chemicals in flea control products. The reviewers knew of no evidence that it has had an interaction with other chemicals. However, it is noted that the proposed 11.8% concentration is higher than other products listed in REFS. The remainder of the CAS Committee was polled via email about the study classification; they also recommended the study be classified as acceptable.

In addition, it is noted that the April 12, 2000 Memorandum from Masih Hashim to Ann Sibold does not include methoprene as an active ingredient in the product. Also, under Background, it states that the product was applied to 6F kittens, whereas both sexes were used in the study.

Prepared by Virginia A. Dobozy, V.M.D., M.P.H.
Reregistration Branch 1, HED (7509C)

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