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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

12/22/1998

MEMORANDUM

SUBJECT: Secondary Review of DERs for Companion Animal Safety Studies

DP Barcodes: D251467, D251468, D251469
PC Codes: 057801, 109701, 129032

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer
Reregistration Branch I, Health Effects Division (7509C) Virginia A Dobozy 12/22/98

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

Action Requested: Provide secondary review of DERs for MRIDs 44078702, 44412601 and 44522102

Recommendation: The HED Companion Animal Safety Committee met on December 16, 1998, to discuss the above DERs. See attached minutes of that meeting.

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MINUTES OF COMPANION ANIMAL SAFETY (CAS) COMMITTEE MEETING
DECEMBER 16, 1998

The following DERs prepared by the Technical Review Branch (RD) were discussed:

1) DP Barcode: D251469; MRID: 44078702; PC Code: 129032

Product: Flea Ovisterilant Collar/Knockout IGR Collar for Dogs and Puppies

Study Title: Safety - Ins. 35.4

In this study, 8 mixed breed dogs/sex/group were treated with either 1 (1x) or 5 (5x) collars containing 0.5% pyriproxyfen (Nylar) for 49 days. Three males and three females served as vehicle controls. Physical examinations and clinical pathology parameters were measured on days -14, 14, 42 and 56. Body weights were measured daily on days -14 to 0 and weekly thereafter.

The study was complicated by signs of ill health in animals of all groups. Pre-treatment, five dogs had either blood in the stool or discharge from the eyes. Post-treatment, 7/8 dogs in the 5x group had eye discharge and 5/8 had blood in the feces. A presumptive diagnosis of coccidiosis was made and two dogs were treated. In the 1x group, 2/8 dogs had eye discharge and 5/8 had bloody feces; 4 were treated for coccidiosis. In the control group, 2/8 had eye discharge, 1/8 had a staph infection and was treated with sulfas, 2/8 were treated for coccidiosis and 12/23 were treated for a *Toxocara leonina* infection. One animal in the 1x group died. The gross necropsy report states that death was due to dehydration and blood loss, possibly due to a *Coccidia* infection.

CAS Committee Recommendations: The DER prepared by the Technical Review Branch (RD) concluded that the study was unacceptable due to the questionable health of the test animals. The HED CAS Committee concurs with this evaluation. The study is also unacceptable due to the use of concomitant treatment for the *Coccidia, Toxocara* and staph infections. Since all animals were not treated for these conditions, the effect of the medications on the toxicity of the test material cannot be dismissed. Other deviations from the Companion Animal Safety Study Guidelines (870.7200) were not discussed because of the unacceptability of the study.

2) DP Barcode: D251467; MRID: 44412601; PC Codes: 109701, 129032

Product: Ecto Flea and Tick Insecticide with IGR (45% permethrin, 5% pyriproxyfen)

Study Title: Target Animal Safety Evaluation of Ecto Flea and Tick Insecticide with IGR in Puppies

In this study, 6 beagle or mixed breed dogs (age 11-12 weeks)/sex/group were treated with either 1, 3 or 5x the recommended dose of Ecto Flea and Tick Insecticide with IGR twice (Days 0 and 21). Controls received deionized water. Clinical observations were conducted daily from Days 0

to 35. The skin at the dose site was examined on the day of treatment and for three to four days thereafter. Body weights were recorded on Days -14, -7, -1, 7, 14, 21, 28 and 35. Food consumption was recorded daily for pens of 3 dogs per sex. Hematology and clinical chemistry parameters were measured pretreatment and on Day 1. Due to slight increases in total bilirubin in the 3x group, additional samples were measured for this parameter on Days 18 and 22. The study results support a 5x margin of safety for the product.

CAS Committee Recommendation: The Committee agreed with the Technical Review Branch's conclusion that the study was acceptable. It was recommended that the Executive Summary be revised to state that the 5x margin of safety is established for puppies less than 12 weeks old. The study is Acceptable for aforementioned age group of dogs. Any reference to older dogs in the body of the Executive Summary should be deleted.

3) DP Barcode: D251468; MRID: 44522102; PC Codes: 057801, 129032

Product: Diazinon-pyriproxyfen collar (15% diazinon; 2.5% pyriproxyfen)

Study Title: Target Animal Safety Evaluation of Combination Diazinon-pyriproxyfen Collars on Puppies

In this study, 6 beagle puppies (10-11 weeks)/sex/group were fitted with either 1, 3 or 5 collars for 60 days. Controls were untreated. Hematology and clinical chemistry parameters were measured on Days -5, 1, 7, 14, 30 and 60. Clinical observations were conducted daily on Day 0 through Day 78. The skin around the collar site was examined daily on Days 0 through 5. Body weights were recorded on Days -14, -7, -1, 7, 14, 21, 28, 35, 42, 49, 56, 60, 74 and 78. Food consumption was recorded daily from Day 0 through 59. There were no clinical signs of toxicity. On Day 1, male and female serum cholinesterase values were reduced 45 and 22%, respectively, for the 1x group; in the 3x group, 83 and 70%; and in the 5x group, 75 and 58%. On Day 7, serum cholinesterase values were decreased 90% or more in all treatment groups. They remained depressed (>75%) until Day 74, 14 days after removal of the collars. RBC cholinesterase values were essentially unchanged.

CAS Committee Recommendations: The Committee agreed with the Technical Review Branch's conclusion that the study was acceptable. Since the product was only tested in puppies, there should be an additional study in adults, if the product is so labeled. There was concern expressed about the degree of plasma cholinesterase suppression, even in the 1x group. The question of the significance of plasma cholinesterase has been discussed previously between HED and RD. In a June 5, 1992 memo from the Director of RD to the Director of HED, RD stated that it has been Agency practice to approve registration of pet collars containing organophosphates when only plasma cholinesterase is inhibited without other overt signs of toxicity or RBC cholinesterase inhibition. PR Notice 96-6 requires the following statement on pet products containing cholinesterase-inhibiting chemicals, "Do not use this product on animals simultaneously or

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within 30 days before or after treatment with or exposure to cholinesterase inhibiting drugs, pesticides or chemicals. However, flea and tick collars may be immediately replaced." It should be noted in the only recovery measurement (14 days after collar removal) plasma cholinesterase values were near normal levels. The labeling would allow collars to be replaced immediately. Based on the data from this study, cholinesterase levels could still be depressed immediately after collar removal.

Members Attending: Byron Backus (RD), Virginia Dobozy (HED), Kit Farwell (HED), Eugenia McAndrew (RD), Guruva Reddy (HED)

Prepared by Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 12/22/98

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