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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: October 12, 2005

MEMORANDUM

Subject: EPA File Symbol: 2517-IN^DSERGEANT'S CYPHENOTHHRIN + IGR
SQUEEZE-ON FOR DOGS
DP Barcode: D321227
Decision No.: 338118
PC Codes: 129013 Cyphenothrin (CAS #39515-40-7), 129032
Pyriproxyfen (CAS #95737-68-1)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
10-12-2005
Byron T. Backus

To: George LaRocca RM 13
Insecticide Branch
Registration Division (7505C)

Applicant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION DECLARATION FROM LABEL:

<u>Active Ingredient(s):</u>	% by wt
Cyphenothrin (CAS #39515-40-7).....	40.0%
Nylar (CAS #95737-68-1).....	2.0%
<u>Inert Ingredients:</u>	58.0%
	Total: 100.00%

ACTION REQUESTED:

The Risk Manager requests:

"...The registrant is providing additional data we discussed at the 7/13/05 meeting."

"...You completed review of the companion animal safety study for 2517-IN, IL on Nov. 30th and Nov. 24th, 2004. Mark Suarez completed review of efficacy data (MRID 46166109) associated with these two products and noted symptoms reported in all dogs in Test Group 2 (see attached excerpt). This appears to be inconsistent with what you reported. Mark has electronically sent you a copy of the efficacy study for further consideration."

BACKGROUND:

There have been two previous TRB toxicity reviews for this product. The first (November 24, 2004) consisted of a review of 5 acute toxicity studies (the inhalation study requirement was waived) and a companion animal (including both adult dogs and 12-week-old puppies) safety study (MRID 46166108). All studies were classified as acceptable. In the companion animal safety study the only possible systemic effects that were observed following exposure to the test material at 5X were ocular discharge and salivation. No effects were noted at 1X (3X was not tested).

Subsequently (memorandum dated June 27, 2005), TRB reviewed findings from an efficacy study (MRID 46166109) in which all 6 dogs treated at what was supposedly a 1X dose showed symptoms which included head shaking and/or slight body tremors. A listing of the symptoms in individual dogs is given below:

Dog Number	Sex [(S)=Spayed]	Symptoms ^a
HHCAVJ	F(S)	Head shaking on Day 3; Slight body tremors on Day 3.
35022	M	Vomiting (Day 1); Head shaking (Days 2, 3 & 5); Licking of paws (Days 2-6); Rubbing of head and body (Day 3); Slight tremors all over body on Day 5.
CNJAZF	F(S)	Slight tremors on Day 1; Shaking on Days 1-5; Squinting on Day 1; Licking of Paws Days 3-5; Unsteadiness Day 1, Circling on Day 2; Pacing on Day 4; Rubbing of head on Day 1.
36737	F	Ear twitching Days 1-3; Head shaking on Days 1 & 3; Licking of paws on Days 1 & 5; Pacing on Days 4 & 5; Slight body tremors Days 2 & 3.
28625	F(S)	Head shaking Days 1-3, 5, 7 & 8; Ear twitching on Day 3, Licking of the paws and genitalia Days 3-4; Hair loss and irritated skin on the right shoulder onto the mid-back on Days 22-47.
34911	M	Vomiting on Day 1; Head shaking Days 1-4, 7-8; Licking of genitalia and/or paws Days 1-7; Hair loss/redness at ear tips on Days 2-5 and 7-33.

^aSymptoms are reported (in text) on p. 19 of MRID 46166109.

There was a meeting with the registrant on 7/13/05, and the registrant has provided (letter dated July 29, 2005) additional information relating to these findings, including the following:

"...The last efficacy study (MRID 46166109) did include observations of effects at a 100 mg/kg (1X) application rate. The reported effects included effects that can be considered normal dog behavior, accentuated under laboratory confinement conditions (i.e., licking of paws and genitalia, pacing, head shaking). Additionally, vomiting is also not uncommon in dogs, under laboratory conditions. Tremors were also observed in this study. The tremors could be based on neurologic pathophysiology or they could be the result of just shaking to relieve itch or an unusual skin sensation. This study was not set up to determine the reason of such effects on the animals tested; however, it did report them in detail. We also believe that some of the reporting may be accentuated by the individual observer and that some of the effects may not have been reported at another laboratory that might consider such activities as normal animal behavior.

"Based on Sergeant's review of the Companion Animal Safety Study and the various application groups...Sergeant's would like to set a minimum weight of five pounds for dogs being treated with Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs. This will ensure that the application rate is within reason of the recommended application rate of 100 mg/kg. It will also allow Sergeant's to develop a product especially for dogs under five pounds..."

The material received also includes the following: "Cyphenothrin, like other later generation synthetic pyrethroids...are strongly contraindicated on cats because of the cat's exquisitely sensitive dermal sensory system that leads to self grooming and ingestion of the product with an often fatal outcome. The behavior of the dogs in this study are reminiscent of this phenomenon observed in cats, although much less severe than in cats. It is probably that the observed effects in the this study were caused by transient cutaneous nerve stimulation in the treated dogs and their ability (as confined, bored animals without other distractions) to apply their full-undivided attention to this issue..."

COMMENTS AND RECOMMENDATIONS:

1. The most likely explanation for the symptoms (including tremors) observed in the efficacy study was that the dogs ingested some of the test material after application.
2. Current directions for the application of this product specify to apply as a stripe from the back of the neck to base of the tail. If labeling is revised to specify application of the product from the back of the neck to a point midway between the neck and tail then the dog would not be able to reach any part of the application site and so would be unable to ingest the product by licking. With this labeling revision, TRB would have no objections to the registration of the proposed product.