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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: June 27, 2005

MEMORANDUM

Subject: EPA File Symbol: 2517-IN SERGEANT'S CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS
DP Barcode: D317320
Decision No.: 338118
PC Codes: 129013 Cyphenothrin (CAS #39515-40-7), 129032 Pyriproxyfen (CAS #95737-68-1)

From: Byron T. Backus, Ph.D. Byron T. Backus 6-27-05 JCR
Technical Review Branch
Registration Division (7505C)

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

Applicant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION DECLARATION FROM LABEL:

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

ACTION REQUESTED:

The Risk Manager requests:

"...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:

This review compares the findings in the previously reviewed companion animal safety study (MRID 46166108) with those of the efficacy data (MRID 46166109) on this proposed product.

COMMENTS AND RECOMMENDATIONS:

1. In the companion animal safety study (MRID 46166108) no symptoms were observed in the 1X dogs; at the 5X dose level possible systemic effects included ocular discharge and salivation, and there was a slight mean weight decrease in this group in the period from Day -3 to Day 7. However, there were no indications of neurological symptoms (including tremors, shaking, head shaking) in the 5X group. In contrast, in the efficacy study (MRID 46166109), all 6 dogs treated at what was supposedly a 1X dose showed symptoms (including those of a neurological nature), as indicated 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.

[a]Symptoms are reported (in text) on p. 19 of MRID 46166109.

2. In the companion animal safety study (MRID 46166108) at 1X dogs weighing <6.6 kg (all puppies) were treated with 1.17 mL (the amount of material that could be applied from a 1.5 mL ampule) test material; those weighing from 6.8-15 kg were also treated with 1.17 mL; those weighing 15.1-29.5 kg were treated with 2.34 mL (2 x 1.17 mL),

while those weighing >29.5 kg were treated with 3.51 mL (3 x 1.17 mL). At the 5X dose level puppies weighing <6.6 kg were treated with 5.85 mL (5 x 1.17 mL); dogs weighing 6.8-15 kg were also treated with 5.85 mL; dogs weighing 15.1-29.5 kg were treated with 11.7 mL (10 x 1.17 mL) and dogs weighing >29.5 were treated with 17.55 mL (15 x 1.17 mL).

From p. 18 of MRID 46166109: "Two male and four female (three of which were spayed) dogs were allocated to Test Group 2. All dogs had short hair..." The following are the body weights of these dogs and the amount of test material applied:

Dog Number	Sex [(S) = Spayed]	Weight (kg)	Dose (mL)[a]	1X Label Dose (mL)
HHCAVJ	F(S)	10.9	2.5	1.17
35022	M	7.7	1.7	1.17
CNJAZF	F(S)	9.2	2.1	1.17
36737	F	6.8	1.5	1.17
28625	F(S)	12.2	2.8	1.17
34911	M	13.6	3.1	1.17

[a]Individual dosages in the efficacy study are presented on p. 31 of MRID 46166109.

In the efficacy study (MRID 46166109) dogs were then treated with from 1.45X to 2.65X the indicated label dosage rate (the mean dose of 2.3 mL was 1.97X the indicated label dosage rate; according to information on p. 84 of MRID 46166109 the dosage rate in the efficacy study was 100 mg cyphenothrin/kg b.w.). The 5X dogs in the companion animal safety study weighing 6.8 - 15 kg were treated with 5.85 mL, or about 2.54X the dose that animals received in the efficacy study.

3. There are obviously then some significant inconsistencies between the findings of the companion animal safety study in MRID 46166108 and the efficacy study in MRID 46166109. The occurrence of neurological signs of toxicity in all 6 dogs in the efficacy study suggests that there is not even a 2X margin of safety associated with the proposed application rate of 1.17 mL in at least some dogs weighing from 6.8 - 15 kg, while the efficacy study data, as submitted, were conducted using a dose rate higher than that of the previously reviewed proposed label.

4. The registrant should be informed of these inconsistencies. The proposed product should not be registered until the issues (margin of safety involved in the use of this product, whether the efficacy data, using a higher dose application rate than that of the proposed label, can be used to support this registration) raised by these inconsistencies have been adequately addressed.