

US EPA ARCHIVE DOCUMENT



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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

December 3, 2010

MEMORANDUM

Subject: Name of Pesticide Product: SERGEANT'S FIPRONIL + CYPHENOTHHRIN
SQUEEZE-ON FOR DOGS
EPA Reg. No. /File Symbol: 2517-RUN
DP Barcode: DP 380758
Decision No.: 435798
Action Code: R310
PC Codes: 129121 (Fipronil: 9.8%)
129013 (Cyphenothrin: 5%)

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

Byron T. Backus
Dec. 3 2010
at Hashi

To: Bonaventure Akinlosotu/Richard Gebken RM 10
Insecticide Branch
Registration Division (7505P)

Registrant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>		<u>% by wt.</u>
129121 Fipronil		9.8
129013 Cyphenothrin		5.0
<u>Other Ingredient(s):</u>		<u>85.2</u>
	TOTAL	100.0

ACTION REQUESTED: The Risk Manager requests:

“For your review: MRID 48129614 for an R310, new EP...”

BACKGROUND:

The material received for review includes an 8-point response (in MRID 48129614) to a previous EPA review (DP 371676, dated February 24, 2010) of the study in MRID 47849609.

COMMENTS AND RECOMMENDATIONS:

1. From p. 5 of MRID 48129614: “As background information, Sergeant’s submitted MRID 47849609 to support an application for registration of an etofenprox spot-on product. EPA initially rejected the study... Sergeant’s provided a rebuttal to the EPA DER, and EPA upgraded the study and granted the requested etofenprox registration. Since MRID No. 47849609 also included a 9.8% fipronil/8.2% cyphenothrin test substance, that study is also being used to support the current submission which is a 9.8% fipronil/5.0% cyphenothrin product.”
2. [Response 1]: According to the EPA memorandum dated April 29, 2010: “We can accept the registrant’s arguments regarding the number of dogs (combining Groups A2 and B3) treated at a 5X dosage rate with Substance II (55.16% w/w etofenprox, 8.78% w/w S-methoprene, 2.31% pyriproxyfen).” Group A2 (consisting of six 10-15 week old puppies) was also treated with 5 applications of Test substance IA, which contained 8.2% cyphenothrin and 9.8% fipronil, while Group B2 (consisting of 6 adult dogs) was treated with 5 applications of Test substance IA and five applications of Test substance III (containing 8.9% S-Methoprene and 2.31% Pyriproxyfen).
3. [Responses 2, 4, and 6]: These are not relevant to the fipronil, cyphenothrin and IGR products.
4. [Response 3]: From p. 2 of the EPA memorandum dated February 24, 2010: “Cumulative dosage rates were...” The material in MRID 48129614 includes (p. 28-29) Table 1 with calculations of the amounts of fipronyl and cyphenothrin delivered to the test subjects. The 5X (Group B2) adults received dosages ranging from 34.49 to 69.12 mg fipronyl/kg and 28.86 to 57.83 mg cyphenothrin/kg, with means of 44.4 mg fipronyl/kg and 37.1 mg cyphenothrin/kg. The 5X (Group A2) puppies received dosages ranging from 175.00 to 184.75 mg fipronyl/kg and 146.43 to 154.59 mg cyphenothrin/kg, with means of 180.0 mg fipronyl/kg and 150.6 mg cyphenothrin/kg. Table 2 (p. 30) gives dosage rates for the actives based on proposed application rates; a 4 lb [1.8 kg] dog or puppy would be dosed with 0.67 mL of formulation [it is assumed by this reviewer that the density is 1.03 g/cm³] containing 67.6 mg fipronyl and 34.5 mg cyphenothrin; dividing these values by 1.8 kg gives 37.6 mg fipronyl/kg and 19.2 mg cyphenothrin/kg, consistent with the 38.0 mg fipronyl/kg and 19.4 mg cyphenothrin/kg given in Table 2. The mean dosages for the 5X (Group A2) puppies are 4.74X (for the fipronyl) and 7.76X (for the cyphenothrin) these values.
5. [Response 5]: In the EPA review of February 24, 2010 it was stated [p. 6] that: “For the puppies, it is impossible to compare and interpret differences in body weight gains when there was such a range in ages (10-15 weeks with no information as to specific ages for individual animals), the dogs were mixed breed and the two heaviest puppies... which would be expected to show the greatest weight gains, were both in the control group.” The registrant’s response has been to provide (p. 31-32 of MRID 48129614) individual ages and weights at the time of treatment, as well as weights on days 7 and 14. From p. 26 of MRID 48129614: “Ages on day of treatment ranged from 73 days (10 weeks) to 106 days (15 weeks), with mean group ages of 12.5

weeks (group A1), 13.1 weeks (group A2) and 14.1 weeks (group C1). There were no significant differences between these groups' ages ($P > 0.05$). The group weights of the puppies at time of treatment were analyzed...and found not to be significantly different ($P > 0.05$).

Weight gains by the puppies over the duration of the study were shown not to be statistically different... The proposed labels read "for dogs and puppies 12 weeks and older"...

Examination of the data in Table 3 (p. 31 of MRID 48129614) indicates that 2 puppies in group A2 (5X dosage) were less than 12 weeks of age (73 and 79 days old) at treatment, two were slightly more than 12 weeks of age (both 87 days old), one was 91 days old and the sixth was 106 days old, with a mean age of 87.17 days (12.45 weeks). This is adequate to allow a 12 week and older claim.

6. [Response 7]: In the EPA review of February 24, 2010 it was stated that: "TRB considers the behavioral changes (running and circling immediately after application of the test substance) in 7 animals (one adult, 6 puppies) as an adverse effect. It is noted that the animals showing behavioral changes were all exposed to test material IA (8.20% cyphenothrin, 9.8% fipronil, either in combination with material III...for the one adult, or in combination with material II...for the puppies). Although the four puppies in Group A2...showed running and circling only after the first application of the test substance and not after the second, third, fourth or fifth application, this may simply be an indication that the application area had been numbed." The registrant's response is that the investigator has stated that such behavior is common when laboratory dogs are restrained or handled and any wet or cold substance is applied to the back. "They try to run away but since they are in a cage they can only move in a circular motion due to the physical constraints of the cage. This fleeing from the handler was very brief (one or two turns), was not accompanied by any vocalization, scratching of, or attempt to lick, the application area. The investigator...considers this behavior not to be evidence of toxicity or an adverse effect. The fact that the sequential 4 applications to the 5X dogs and puppies did not induce this "escape" behavior indicates the dogs quickly accommodated to the application since they did not perceive the procedure of reapplying the test substances as irritating, itchy or painful and there was no evidence of subsequent dermal pathologic change. The proposal by the reviewer that the test substances had any analgesic or topical anesthetic properties that "numbed" the area is unsupported and presumptuous conjecture."

The material in MRID 48129614 includes (p. 33) a letter dated 11 March 2010 from the performing laboratory (ClinVet), includes the following: "Two of six puppies in Group A1 and four of six in group A2 did some running in circles immediately after application. It lasted one or two circles in the pen and then they calmed down. No scratching or attempts at licking. No vocalization. Our impression was that the puppies were stimulated by the application of the licking. They got used to the effect of being wet and no similar signs were seen after the following application..."

It is concluded that the running and circling of one dog and four puppies following the initial application of test material is a startle reaction rather than a toxicological response, and that there was no indication then that any of the test subjects showed any toxicological response at the 5X dose level.

7. [Response 8]: The review of February 24, 2010 included the comment [p. 15] that application sites had an oily or wet appearance and that persistence of test substance on the hair of dogs for

more than 14 days is of concern due to potential human exposure. The registrant's response includes the statement: "EPA has conducted risk assessments and determined that the intended exposure for each of the active ingredients in test substance II is acceptable in currently registered products."

8. After examining the registrant's responses in MRID 48129614 to the EPA review of February 24, 2010, TRB concludes that the issues raised in that review have been adequately addressed by the material in MRID 48129614, and that the study (MRID 47849609) findings for Groups B1, B2, A1 and A2 adequately satisfy the 870.7200 (companion animal safety) data requirement for both adult dogs and puppies 12 weeks of age and older for EPA File Symbol 2517-RUN (9.8% fipronil + 5.0% cyphenothrin) at the proposed dose levels. The study in MRID 47849609 has previously (April 29, 2010) been classified as **Acceptable/Guideline** to satisfy the guideline requirement for a companion animal safety study (ORRTS 870.7200) for a formulation (2517-RGG) containing 55% Etofenprox and 2.2% Pyriproxyfen.