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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

April 29, 2010

MEMORANDUM

Subject:	Name of Pesticide Product:	ETOFENPROX/NYLAR SPOT-ON FLEA AND TICK FOR DOGS AND PUPPIES
	EPA Reg. No. /File Symbol:	2517-RGG
	DP Barcode:	DP 376746
	Decision No.:	420097
	Action Code:	R310
	PC Codes:	128965 (Etofenprox: 55%) 129032 (Pyriproxyfen: 2.2%)

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

Byron T. Backus
4-29-2010

To: Kevin Sweeney/Richard Gebken, RM 13
Insecticide Branch
Registration Division (7505P)

Registrant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION FROM LABEL:

Active Ingredient(s):	By wt.
128965 Etofenprox	55.00%
129032 Pyriproxyfen	2.20%
Other Ingredient(s):	42.80%
TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"TOX: Review response to companion animal safety review."

BACKGROUND:

The material received includes responses to comments in a previous TRB review (February 24, 2010) of a companion animal safety study (MRID 47849609). In addition, there is a label (dated 10 September 2009) which indicates a dosage rate of 2.0 mL for small dogs weighing from 4 to 20 lbs.

COMMENTS AND RECOMMENDATIONS:

1. We can accept the registrant's arguments regarding the numbers 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).

2. While we would have preferred to have two separate studies (one with puppies, the other with adult dogs), the current 870.7200 Companion Animal Safety Guidelines state: "The age of animals in the study is dependant upon label claims. If only adults (6 months or older) are the targeted population of animals to receive treatment, adults only will suffice. However, if a product is registered for use on pediatric animals (i.e. puppies…), the label should state a minimum age for this group, for example, "Do not use on puppies…less than eight weeks of age". Consequently, the product should be tested in 8 week-old animals in the companion animal safety study." There is the additional stipulation: "At least six animals per sex should be used at each dosage level."

3. From the original study report, Group A1 puppies weighed from 4.66 to 12.23 lb (2.12 to 5.56 kg) and were dosed once with from 3.1 to 7.5 mL [or from 1.5 to 3.75X the dosage rate of 2.0 mL] Substance II, while Group A2 puppies weighed from 5.94 to 16.1 lb (2.7 to 7.32 kg) and were dosed with cumulative amounts of 18.8 to 50 mL [or from 9.4 to 25X the dosage rate of 2.0 mL] Substance II. One Group B3 adult weighed 8.95 lbs (4.06 kg) and was treated with a cumulative amount of 12.5 mL (5 x 2.5 mL, or 7.5X the dosage rate of 2.0 mL), while the remaining B3 dogs weighed from 15.4 to 20.1 lb (7.0 to 9.1 kg) and were each treated with a cumulative amount of 22.5 mL (5 x 4.5 mL, or 11.25X the dosage rate of 2.0 mL) Substance II.

4. The registrant has presented statistics (Table 4) evaluating the % change body weight/day for the different puppy groups. These statistics show no significant differences between Groups A1, A2, and their controls (C1) with respect to this parameter for the periods from day 1 to 7, 7-14, and for 1-14.

5. The registrant has presented statistics (Table 3) evaluating the % change body weight/day for Group B3 and C2 (a control group) adult dogs. These statistics show a significant difference ($P < 0.05$) between these groups (with Group B3 showing reduced gains) with respect to this parameter for the periods from day 1 to 7 and from day 1 to 14 (but no significance for the period from day 7-14). This has to be considered an effect of exposure. From the original study report (see p. 36 of MRID 47849609) it is noted that individual daily food consumption was not reported in grams but by a scoring system (Fc 1 = 0-25%, Fc 2 >25-50%, Fc 3 >50-75%, and Fc 4 > 75-100%), and it is considered unlikely by this reviewer that the resulting data would be robust enough to show whether or not a moderate drop in food consumption actually occurred in the B3 (or any) group from day 1 to 7.

6. The material from the registrant includes (Table 5) a listing of the ages of the puppies. Group A2 ranged from 73 to 106 days (mean: 87.2), with only two puppies 84 days (12 weeks) of age or less. Group A1 ranged from 79 to 99 days (mean: 91.5), with only one puppy 84 days (12 weeks) of age or less. Group C1 ranged from 91-106 days of age. It is recommended that the proposed label treatment age be raised from 12 to 13 weeks (or to 3 months).

7. The registrant has provided a comment (letter dated 11 March 2010) from the investigator regarding the behavioral effect (response?) in some puppies immediately following topical application. According to this letter: "Two of six puppies in 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 a liquid. They got used to the effect of being wet and no similar signs were seen after the following applications…" However, the response also includes the following: "The question that needs is answering is "why only the test item groups"?... A subjective conclusion was that the test items may have been cold (or felt cold, maybe as a result of evaporation?). That could be the reason why the pups did not react after the next applications and also why no signs were seen on the skin and why no other changes were recorded…"

Since this effect was not seen in controls, it has to be considered an effect of the test substance. As there were no indications of scratching or licking at the application site, no vocalization, and the puppies calmed down within a short period of time, it can be considered a minor effect. However, it is recommended that there be a statement on the label noting this effect can occur but that the dog should quickly calm down.

8. The revised executive summary (incorporating the above comments) is attached. The study is upgraded to Acceptable.

9. TRB concludes that the companion animal safety study in MRID 47849609 will support the proposed dosage rate of 2.0 mL (of the formulation containing 55% Etofenprox and 2.2% Pyriproxyfen) on 4-20 lb dogs with retreatment at monthly (30-day) intervals.

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

Signature: Byron T. Backus
Date: 04-29-2010

EPA Secondary Reviewer: Ayaad Assad, DVM, Ph.D.
Toxicology and Epidemiology Branch, HED (7509P)

Signature: A. Assad
Date: 04/29/2010

Template version 02/06

DATA EVALUATION RECORD

Note: This document contains only a revised Executive Summary

STUDY TYPE: Companion animal safety study- dogs/puppies – OPPTS 870.7200

PC CODE: 128965- Ethofenprox, 129032- Pyriproxyfen, **DP BARCODE:** 371676

TEST MATERIAL (PURITY): Cyphenothrin (8.2% w/w), Fipronil (9.8% m/w), Etofenprox (55.16% w/w), S-Methoprene (8.78% w/w), Methoprene (8.90% w/w) and Pyriproxifen (2.31% and 2.43% w/w)

TRADE NAME: Not provided

CITATION: Delport, P.C. (2009) Companion animal safety evaluation on dogs of spot-on products containing multiple toxicants and insect growth regulators. ClinVet International (Pty) Ltd., Bloemfontein, Republic of South Africa. Study No. CV 08/551, August 6, 2009. MRID 47849609. Unpublished.

Miller, T. (2010) Response to February 24th, 2010, Decision 420097, 2517-RGG, Re: Etofenprox/Nylar Spot-On Flea & Tick for Dogs and Puppies.

SPONSOR: Sergeant's Pet Care Products, Plano, Texas

REVISED EXECUTIVE SUMMARY: In a companion animal safety study (MRID 47849609), groups of random-source adult (> 6 months of age) and juvenile (10-15 weeks of age) dogs were topically administered 3 combinations of insecticides and insect growth regulators or one inert substance. Two groups of three male and three female juvenile dogs were administered test substance IA (8.2% w/w cyphenothrin and 9.8% m/w fipronil; Batch No. 012003-09) and test substance II (55.16% w/w etofenprox, 8.78% w/w s-methoprene and 2.31% w/w pyriproxifen; Batch No. 011901-09) at either 1X (recommended dose) or 5X (recommended dose hourly for 5 applications). The test substances were applied simultaneously as adjacent stripes along the dorsum of the dog from behind the ears caudally to the base of the tail. Two groups of three male and three female adult dogs weighing 9-20 kg were administered the test substance IA and test substance III (8.90% w/w methoprene and 2.43% w/w pyriproxifen; Batch No. 011902-09) at either 1X (recommended dose) or 5X (recommended dose hourly for 5

applications). The test substances were applied as previously described. A group of three male and three female adult dogs weighing less than 9 kg was administered test substance II at 5X (recommended dose hourly for 5 applications). A group of three male and three female juvenile dogs and another group of three male and three female adult dogs were administered control substance IVA (Batch No. 012004-09) containing inert ingredients (not otherwise stated) at 5X the recommended dose. The groups and test materials they received are shown in the table below:

Group			
A	Group A1 (n=6) Puppies (10-15 weeks) Single application of substance IA Single application of substance II	Group A2 (n=6) Puppies (10-15 weeks) Five applications of substance IA Five applications of substance II	
B	Group B1 (n=6) Adults (9-20 kg) Single application of substance IA Single application of substance III	Group B2 (n=6) Adults (9-20 kg) Five applications of substance IA Five applications of substance III	Group B3 (n=6) Adults (<9 kg) Five applications of substance II
C	Group C1 (n=6) Puppies (10-15 weeks) Five applications control substance IVA	Group C2 (n=6) Adults (9-20 kg) Five applications control of substance IVA	

Substance IA contains 8.2% w/w cyphenothrin and 9.8% m/w fipronil.
Substance II contains 55.16% w/w etofenprox, 8.78% w/w s-methoprene, 2.31% w/w pyriproxifen.
Substance III contains 8.90% methoprene, 2.43% w/w pyriproxifen.
Control substance IVA contains inert control substances.

The animals were observed for clinical signs of toxicity and dermal irritation for four hours post-application and then twice daily for the duration of the study (14 days post-application). Body weight, body weight gain, food consumption and clinical pathology parameters (hematology and clinical chemistry) were measured at the required intervals.

All animals survived to the end of the study. Immediately after treatment, one adult dog in Group B1 (1X applications of test substances IA and III) showed behavioral changes (running, circling). This behavioral change was not considered treatment-related in adults by the sponsor since it was not observed at 5X the recommended dose. Immediately after treatment, two puppies in Group A1 (1X application of test substances IA and II) showed behavioral changes (running, circling). Four puppies in Group A2 (5X application of test substances IA and II) showed similar behavioral changes after the first application but not after subsequent applications. These behavioral changes are considered to be an adverse effect. White crystallization was observed on the hair tips of many adult and juvenile dogs in the treated and control groups. The application sites of all dogs in Group B3 (5X application of test substance II) had an oily or wet appearance. The sign disappeared from one dog on Day +14 but was present on all others at the end of the study.

All adult dogs and puppies gained weight from Day -1 to Day 14. However, mean weight gain in pups in the treated groups (A1 and A2) was 15% lower than the control group pups, although statistics evaluating the % change body weight/day show no significant differences between Groups A1, A2, and their controls (C1) with respect to this parameter for the periods from day 1 to 7, 7 to 14, and for 1 to 14. The mean weight gain in the treated adult animals (Groups B1, B2 and B3) was decreased (30-99% as compared to the control group). The difference relative to controls was largest in the smaller adult dogs in Group B3 (99% decrease as compared to the control group). Statistics evaluating the % change body weight/day for Groups B3 and their C2 controls show a significant difference ($P<0.05$) between these groups (with Group B3 showing

reduced gains) with respect to this parameter from day 1 to 7 and from day 1 to 14 (but with no significance for the period from day 7 to 14). Individual food consumption was not reported in grams but by a scoring system (Fc 1 = 0-25%, Fc 2>25-50%, Fc 3 >50-75%, and Fc 75-100%) and it is considered unlikely by this reviewer that the resulting data would be robust enough to show whether a moderate drop in food consumption occurred actually occurred in the B3 (or any) group from day 1 to 7. No treatment-related hematology or clinical chemistry changes were observed.

Seven animals (one adult, 6 puppies) showed behavioral changes (characterized as running and circling) immediately after the first application of the test substance. They were all exposed (applied "simultaneously") to test material IA (8.20% cyphenothrin, 9.8% fipronil, either in combination with material III, 8.90% methoprene and 2.43% pyriproxyfen, for the one adult, or in combination with material II, 55.16% etofenprox, 8.78% methoprene and 2.31% pyriproxyfen for the puppies). The registrant has provided a comment (letter dated 11 March 2010) from the performing laboratory regarding this response: "Two of six puppies in 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 a liquid. They got used to the effect of being wet and no similar signs were seen after the following applications…" However, the response also includes the following: "The question that needs answering is "why only the test item groups"?... A subjective conclusion was that the test items may have been cold (or felt cold, maybe as a result of evaporation?). That could be the reason why the pups did not react after the next applications and also why no signs were seen on the skin and why no other changes were recorded…"

Since this effect was not observed in controls, it has to be considered an effect of the test substance. As there were no indications of scratching or licking at the application site, no vocalization, and the puppies calmed down within a short period of time, it can be considered a minor effect. However, it is recommended that there be a statement on the label noting this effect can occur but the dog should quickly calm down.

The response from the registrant includes a listing of the ages of the puppies. Group A2 ranged from 73 to 106 days (mean: 87.2), with only two puppies 84 days (12 weeks) of age or less. Group A1 ranged from 79 to 99 days (mean: 91.5), with only one puppy 84 days (12 weeks) of age or less. Group C1 ranged from 91 to 106 days of age. It is recommended that the proposed label treatment age be raised from 12 to 13 weeks (or to 3 months).

It is concluded that although there were possible effects, which consisted of short-term running and circling in 2/6 1X and 4/6 5X puppies – not seen in their controls - following the first application of the test material and reduced weight gains in 5X adult dogs, these were minor. In particular, there were no indications that the puppies were in any pain or distress, and a similar response was not seen in those animals in which there was reapplication. It is recommended that there be a statement on the label noting that the puppy or dog may have a short-term response.

This companion animal safety study in male and female random-source adult dogs and puppies is reclassified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a companion animal safety study (OPPTS 870.7200) on 4-20 lb dogs for a formulation containing 55% Etofenprox and 2.2% Pyriproxyfen with the proposed dosage rate of 2.0 mL with retreatment at monthly (30-day) intervals.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided for ClinVet International. Pathcare Veterinary Laboratory, which conducted the hematology and clinical chemistry analyses, is not GLP accredited but is ISO 15189 certified.