

US EPA ARCHIVE DOCUMENT

PRODUCT PERFORMANCE / EFFICACY REVIEW

Mark Suarez, Entomologist - IB

Mark Suarez
Nov 2006

DATE: 7 November 2006

EPA REG. NUMBER: 2517-IL
2517-IN
2517-ON

PRODUCT NAME: Sergeant's Cyphenothrin Squeeze-On for Dogs [2517-IL]
Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs [2517-IN]
Sergeant's Cyphenothrin + Methoprene Squeeze-On for Dogs [2517-ON]

REGISTRANT: Sergeant's Pet Care Products, Inc.

PM: George LaRocca, PM13
REVIEWER: Linda DeLuise

DECISION #.: 345654 [2517-IL]
338118 [2517-IN]
358246 [2517-ON]

DP BARCODE: 305952 [2517-IL]
305945 [2517-IN]
307614 "
319065 [2517-ON]

ACTION: R26 [2517-IL]
R31 [2517-IN]
R26 [2517-ON]

ACTIVE INGREDIENT(S): 129013, Cyphenothrin.....40.0% [2517-IL]
129013, Cyphenothrin.....40.0% [2517-IN]
129032, Pyriproxyfen.....2.0%
129013, Cyphenothrin.....40.0% [2517-ON]
105402, s-Methoprene.....2.3%

TYPE: Wipe-On (Squeeze-On) for Dogs

OPPTS GUIDELINE(S): 810.1000
810.3000
810.3300

MRID:

46346601
46039501
46041303
46166109
46298501
46298502
42614501
45086801
44948301
44546601
46166110

GLP ?:

No.

SITES:

Dogs; Puppies (≥ 12 weeks old)

PESTS:

Fleas (adult); Fleas (eggs); Fleas (larvae);
Ticks; Mosquitoes; Mosquitoes (vector of
WNV); Mosquitoes (vector of Heartworm);
Deer Ticks (vector of Lyme Disease)

STUDY APPLICATION RATE:

variable (generally 100 mg AI/kg)

LABEL APPLICATION RATE:

Cyphenothrin [All products]:
>50 mg Cyphenothrin per kg dog body
weight for dogs <100 lbs

Pyriproxyfen [2517-IN]:
>2.5 mg Cyphenothrin per kg dog body
weight for dogs <100 lbs

s-Methoprene [2517-ON]:
>2.875 mg Cyphenothrin per kg dog body
weight for dogs <100 lbs

STUDY SUMMARIES:

The registrant submitted and cited a number of studies in support of three new cyphenothrin-based squeeze-on products for the protection of dogs against fleas, ticks, and mosquitoes. Each of these products contains the adulticide cyphenothrin. In addition two of the formulations [2517-IN & 2517-ON] contain an insect growth regulator (IGR). In the case of 2517-IN, the IGR is pyriproxyfen (i.e., Nylar®); in 2517-ON the IGR is s-Methoprene. The incorporation of an IGR is expected to enhance the effectiveness of the products by negatively affecting the development of immature stages of fleas.

Data Submitted in Support of Cyphenothrin Activity

MRID 46166110. Young, D. 2003. Dose Titration of a Cyphenothrin Squeeze-On against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus*) on Dogs. Unpublished study prepared by Thomas A. Miller, Veterinary Research and Regulatory Consultant. 23 p.

The submitted data examined the efficaciousness of two dose rates of cypermethrin against fleas (*Ctenocephalides felis*) and brown dog ticks (*Rhipicephalus sanguineus*) when applied to dogs. The study compared the number of parasites found on test animals following a dose of 0, 25, or 100 mg/kg. Against fleas, the data demonstrate that cyphenothrin provides a greater than 90% reduction, relative to the control group mean, for up to 23 days at the 25 mg/kg rate and 35 days at the 100 mg/kg rate. For the brown dog tick, the data demonstrate that cyphenothrin provides a greater than 90% reduction, relative to the control group mean, for up to 30 days at the 25 mg/kg rate and 44 days at the 100 mg/kg rate. No data were provided for the label application rate of 50 mg/kg.

The study data support label claims of 23 days against fleas and 30 days against brown dog ticks. Because the label rate is twice the lowest dose tested and the data for the higher dose tested the registrant has argued that the product is likely to kill or repel fleas for up to 28 days (4 weeks/1 month). Under the condition that confirmatory data (for fleas and an additional tick species) be submitted within 12 months, a claim of 28 days against fleas and ticks is acceptable.

MRID 44546601. Anderson, K.; Solberg, J. 1998. Product Performance/Efficacy Reports: Evercide Pet and Plant Spray 2648: Lab Project Number: E-3459-97: 10-223-1085: 10-223-1185. Unpublished study prepared by McLaughlin Gormley King Co. 120 p.

From DER dated 27 June 2000 [No electronic copy available; these are the conclusions]:

“The data presented in EPA Accession (MRID) Number 44546601, having been obtained from standard laboratory and kennel testing conducted according to requirements of 95-9(a) subpart (1)-(3) on p. 263 and meeting the standards of 95-9(b)(2)(i) on p. 264 of the Product Performance Guidelines, are adequate to support the claims for killing adult fleas on contact by direct spray as summarized under Tab A in the previously mentioned volume, where a similar formulation was sprayed into a plastic pail

onto *CTENOCEPHALIDES FELIS* adults on white terry cloth at 2 different area rates with 99% mortality in both cases. In a similar manner, the data summarized under Tab B in the volume are adequate to support the claims for killing ticks on contact by direct spray, where the same similar formulation is sprayed onto *RHIPICEPHALUS SANGUINEUS* on filter paper in a glass crystallizing dish with the result that 100% mortality occurred at a standard dosage of 1.0 ml. Additionally, data summarized under Tab C of the volume are adequate to support the claims for killing of fleas for 14 days and ticks for up to 7 days following trigger spray or pump spray application of a similar formulation (with lower concentration of active ingredients) to dogs of mixed sexes and weights and haircoat length as well as breeds at a rate sufficient to wet the coat to saturation, with the result that cat flea mortality was maintained at 100% for 14 days and mortality of American dog tick, *DERMACENTOR VARIABILIS*, was 100% at 3 days but fell to a marginally acceptable 81% at 7 days. Furthermore, data summarized under Tab d of the volume are adequate to support the claims for killing of fleas for 23 days and ticks for 9 days following trigger spray or pump spray application of the same similar formulation as in Tab C to cats of mixed sexes and haircoat length as well as weights at an average rate of 10.75 grams product per kilogram of pet body weight, with the result that cat flea mortality was maintained at 93% or above for 23 days and mortality of brown dog tick was maintained at or above 92% for 9 days. We will accept a claim for rapid knockdown and kill of fleas on dogs following application of the subject product at a rate sufficient to saturate the animal's coat, based on the fact that the similar formulation resulted in 100% mortality of cat fleas at 1 hour after spraying. Finally, we will accept the claim for killing [controlling] deer ticks and other ticks [Ixodid] species that may carry and transmit Lyme disease, on the basis of the fact that both the American dog tick and the brown dog tick are Ixodid ticks plus we have previously accepted similar formulations of permethrin and pyrethrins in combination that were effective against deer tick. -- RL Vern L. McFarland, IB"

The cited MRID could not be considered in support of the subject formulations because the test formulations were not similar to those under consideration. The test formulations contained permethrin and pyrethrins, not cyphenothrin, pyriproxyfen, or s-methoprene.

MRID 46166109. Cruthers, L. 2003. Efficacy Evaluation of a Cyphenothrin Spot On Against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus*), American Dog Ticks (*Dermacentor variabilis*), Nymphal Deer Ticks (*Ixodes scapularis*), and Adult *Aedes aegypti* Mosquitoes on Dogs. Project Number: 0307. Unpublished study prepared by Professional Laboratory and Research and Thomas A. Miller, 342 p.

When applied at a rate of 100 mg/kg, the tested Cyphenothrin Spot-on was greater than 90% effective (based on comb counts) against adult cat fleas, *Ctenocephalides felis*, and nearly 90% effective against American dog ticks, *Dermacentor variabilis*, between test days 3 and 30.

On Test Day 37, this formulation was only ~81% and ~75% effective against adult fleas and ticks. The efficacy against adult fleas was less than ~47% on Test Days 44 and 51 and less than ~69% effective against adult ticks at these same times.

On Test Day 7, this cyphenothrin spot-on formulation was 100% effective against adult fleas at 1, 2 and 3 hours post-infestation and ~83, 89, and 95% effective respectively, against adult American dog ticks at these same time points. The majority of the dead fleas and ticks were found in the pans beneath the dog cages at 1 hour post-infestation on Test Day 7.

Hair removed from dogs treated with this cyphenothrin spot-on formulation killed ~98% of the nymphal deer ticks on Test Day 10 and ~81% of the nymphal deer ticks on Test Day 38. This cyphenothrin spot-on formulation reduced the net percent mosquito landings by ~28%, 19% and 0% on Test Days 9, 30 and 51, respectively. Net percent mosquito mortality (really dead + moribund) was ~96%, 100% and 0% on Test Days 9, 30 and 51, respectively and the net percent reduction in blood-feeding was ~91%, 83% and 6% on Test Days 9, 30 and 51, respectively.

The study dose rate is substantially greater than the label dose rate. The dose rate used in the study was 100 mg AI/kg. The label dose rate is >5.14mg AI/kg, except for dogs less than 0.5 kg. Thus, the study does not support the desired registration.

MRID 46298501. Miller, T. 2003. Effect of Shampoo After Treatment with Cyphenothrin Squeeze-on on Efficacy against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Ticks (*Rhipicephalus sanguineus*) on Dogs: Analysis of Data and Conclusions. Project Number: MS/20D. Unpublished study prepared by Sharp Veterinary Hospital and Vetoquinol N.A., Inc. 15 p.

A squeeze-on formulation containing cyphenothrin was applied once to two groups of dogs that were infested and were subsequently re-infested with adult fleas (*Ctenocephalides felis*) and ticks (*Rhipicephalus sanguineus*). The dose rate was 100 mg/kg. Flea and tick counts were performed at 1 and 2 days after treatment and at 1 and 2 or 3 days after re-infestation. The treated dogs were bathed with low detergent shampoos 12 days after treatment and wetted with water on the 19th day. No significant effect of shampoo on the residual efficacy of the spot-on was observed. Efficacy, at 90% or better compared with untreated controls, was shown against fleas for up to 16 days and against ticks for 30 days. The data appear to support claims against adult fleas for up to 30 days, if the dog is not washed or wetted.

The study dose rate is substantially greater than the label dose rate. The dose rate used in the study was 100 mg AI/kg. The label dose rate is >5.14mg AI/kg, except for dogs less than 0.5 kg. Thus, the study does not support the desired registration.

MRID 46298502. Miller, T. 2003. Competitive Efficacy Evaluation of a Cyphenothrin Spot-On Against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus*) and Against Feeding by *Aedes albopictus* and *Culex quinquefasciatus* Adult Mosquitoes on Dogs. Project Number: MS13D. Unpublished study prepared by Sharp Veterinary Hospital and Vetoquinol N.A., Inc. 25 p.

Squeeze-on formulations containing cyphenothrin, fipronil, or phenothrin were applied once a group of dogs that were infested and were subsequently re-infested with adult fleas (*Ctenocephalides felis*), ticks (*Rhipicephalus sanguineus*), and mosquitoes

(*Aedes albopictus* and *Culex quinquefasciatus*). The dose rate was approximately 100 mg/kg. Flea and tick counts were performed at 1 and 2 days after treatment and at 1 and 2 or 3 days after re-infestation. Efficacy, at 90% or better compared with untreated controls, was shown against fleas and ticks for up to 37 days. For mosquitoes, feeding was reduced by >90%, compared to controls, through 22 DAT. The data appear to support claims against adult fleas for up to 30 days, if the dog is not washed or wetted.

The study dose rate is substantially greater than the label dose rate and the formulation contains 2.3% s-Methoprene, which is not in the formulation of the registration being sought. The dose rate used in the study was 100 mg Cyphenothrin/kg. The label dose rate is >11.012 mg Cyphenothrin/kg, except for dogs less than 1 kg. Thus, the study does not support the desired registration.

MRID 46039501. Cruthers, L. 2003. Efficacy Evaluation of a Permethrin Squeeze-On Against Adult Cat Fleas (*Ctenocephalides Felis*), Adult Brown Dog Ticks (*Rhipicephalus Sanguineus*), Nymphal Deer Ticks (*Ixodes Scapularis*) and Adult *Aedes aegypti* Mosquitoes on Dogs. Project Number: 0243. Unpublished study prepared by Professional Laboratory and Research. 79 p.

The cited study was not applicable to the registration desired. The study examined the efficacy of 45% permethrin formulations against various pet parasites.

MRID 46039501 was not considered in support of the registration of 2517-ON.

MRID 46166109. Cruthers, L. 2003. Efficacy Evaluation of a Cyphenothrin Spot-On Against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus*), American Dog Ticks (*Dermacentor variabilis*), Nymphal Deer Ticks (*Ixodes scapularis*), and Adult *Aedes aegypti* Mosquitoes on Dogs. Project Number: 0307. Unpublished study prepared by Professional Laboratory and Research and Thomas A. Miller, 342 p.

When applied at a rate of 100 mg/kg, the tested Cyphenothrin Spot-on was greater than 90% effective (based on comb counts) against adult cat fleas, *Ctenocephalides felis*, and nearly 90% effective against American dog ticks, *Dermacentor variabilis*, between test days 3 and 30.

On Test Day 37, this formulation was only ~81% and ~75% effective against adult fleas and ticks. The efficacy against adult fleas was less than ~47% on Test Days 44 and 51 and less than ~69% effective against adult ticks at these same times.

On Test Day 7, this cyphenothrin spot-on formulation was 100% effective against adult fleas at 1, 2 and 3 hours post-infestation and ~83, 89, and 95% effective respectively, against adult American dog ticks at these same time points. The majority of the dead fleas and ticks were found in the pans beneath the dog cages at 1 hour post-infestation on Test Day 7.

Hair removed from dogs treated with this cyphenothrin spot-on formulation killed ~98% of the nymphal deer ticks on Test Day 10 and ~81% of the nymphal deer ticks on Test Day 38. This cyphenothrin spot-on formulation reduced the net percent mosquito landings by ~28%, 19% and 0% on Test Days 9, 30 and 51, respectively. Net percent

mosquito mortality (really dead + moribund) was ~96%, 100% and 0% on Test Days 9, 30 and 51, respectively and the net percent reduction in blood-feeding was ~91%, 83% and 6% on Test Days 9, 30 and 51, respectively.

The study dose rate is substantially greater than the label dose rate. The dose rate used in the study was 100 mg AI/kg. The label dose rate is >5.14mg AI/kg, except for dogs less than 0.5 kg. Thus, the study does not support the desired registration.

MRID 46298502. Miller, T. 2003. Competitive Efficacy Evaluation of a Cyphenothrin Spot-On Against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus*) and Against Feeding by *Aedes albopictus* and *Culex quinquefasciatus* Adult Mosquitoes on Dogs. Project Number: MS13D. Unpublished study prepared by Sharp Veterinary Hospital and Vetoquinol N.A., Inc. 25 p.

Squeeze-on formulations containing cyphenothrin, fipronil, or phenothrin were applied once a group of dogs that were infested and were subsequently re-infested with adult fleas (*Ctenocephalides felis*), ticks (*Rhipicephalus sanguineus*), and mosquitoes (*Aedes albopictus* and *Culex quinquefasciatus*). The dose rate was approximately 100 mg/kg. Flea and tick counts were performed at 1 and 2 days after treatment and at 1 and 2 or 3 days after re-infestation. Efficacy, at 90% or better compared with untreated controls, was shown against fleas and ticks for up to 37 days. For mosquitoes, feeding was reduced by >90%, compared to controls, through 22 DAT. The data appear to support claims against adult fleas for up to 30 days, if the dog is not washed or wetted.

The study dose rate is substantially greater than the label dose rate. The dose rate used in the study was 100 mg Cyphenothrin/kg. The label dose rate is approximately > 1/10th the study dose rate, except for dogs less than 1 kg. Thus, the study does not support the desired registration.

Data Submitted in Support of Puriproxyfen Activity

MRID 42684501. Rogosheske, S. 1990. Residual Effectiveness of Nylar on Cat Flea Larvae as a Carpet/Premise Spray: Lab Project Number: F-0122-90. Unpublished study prepared by McLaughlin Gormley King Co. 16 p.

In the cited study, carpet samples infested with cat flea, *Ctenocephalides felis*, larva were treated with pyriproxyfen (Nylar®). Although the application resulted in significant reduction in adult emergence, the biology of the parasite is such that the study does not aid in determination of the effectiveness of a spot-on. (The eggs fall off the animal and larvae hatch on the ground. Thus, the length of egg exposure to treated animal hair may not be adequate for the IGR to demonstrate insecticidal activity.)

MRID 42684501 was not considered in support of the registration of 2517-IN because the test protocol was fundamentally different from the desired use pattern.

MRID 44948301. Schlekau, J. 1999. Product Performance/Efficacy Reports: Nylar Concentrate 2607: Lab Project Number: TL-3095: TL-3096: TL-3097. Unpublished study prepared by McLaughlin Gormley King Co. 61 p.

In the cited study, carpet samples infested with cat flea, *Ctenocephalides felis*, larva were treated with a shampoo or direct spray containing pyriproxyfen (Nylar®). Although the application resulted in significant reduction in adult emergence and notable residual activity for the duration of the study (>90, for 6 to 13 months) months, the biology of the parasite is such that the study does not aid in determination of the effectiveness of a spot-on. (The eggs fall off the animal and larvae hatch on the ground. Thus, the length of egg exposure to treated animal hair may not be adequate for the IGR to demonstrate insecticidal activity.)

MRID 42684501 was not considered in support of the registration of 2517-IN because the test protocol was fundamentally different from the desired use pattern.

MRID 45086801. Donahue, W.; Meola, S.; Palma, K. et al. 2000. Nylar 50 (percent) Concentrate: Product Performance/Efficacy Reports. Unpublished study prepared by McLaughlin Gormley King. 79 p.

From DER dated 27 June 2000:

“CONCLUSIONS & RECOMMENDATIONS The data presented in EPA Accession (MRID) Number 450868-01, having been compiled from standard laboratory and kennel testing conducted according to requirements of § 95-9(a)(1) to (3) on p. 263 and meeting the standard of § 95-9, subpart (b)(2)(i) on p. 264 of the Product Performance Guidelines are adequate to support claims of inhibiting the hatch of larval fleas, killing of flea eggs, inhibiting the hatch of flea eggs and adversely affecting the physiological health of fleas when the subject product is diluted to produce end use products having a active ingredient [pyriproxyfen] concentration of 0.01% and 0.025% as a dip and 0.025% and 0.05% as a shampoo in the testing reported in the portion under Tab 1; are adequate to demonstrate the physiological effects of extremely low concentrations of active ingredient on the molecular structure of flea eggs exposed to pyriproxyfen in glass vials having a deposit of 0.25 mg/cm² as reported in the portion under Tab 2, to the extent that pyriproxyfen prevented cellular differentiation and no blastoderm had formed in eggs that were collected even more than 50 hours after exposure; are adequate to demonstrate the inhibition of egg hatch and emergence of adult fleas when eggs were exposed to either residues of 1.1 mg/cm² on filter paper or the same deposit on aliquots of dog hair, which were prepared by using a standard dilution of 0.007% a.i. solution, or when exposed to dog hair that had been treated with pyriproxyfen as a 0.125% spray, all of which were reported under Tab 3; and are adequate to demonstrate the following physiological effects on adults and eggs of the cat flea, *Ctenocephalides felis*, when adult fleas of both sexes were exposed to 1.1 mg AI/cm² on treated filter paper: histological studies of unfed fleas demonstrated that pyriproxyfen exposure caused depletion of fat body reserves and death by starvation, and fed fleas exposed to pyriproxyfen-treated dog hair also appeared to die of starvation, while eggs deposited by females in these tests were largely empty shells; additionally, studies on flea eggs suggested that pyriproxyfen was less effective as an ovicide than fenoxycarb, that pyriproxyfen exposure of newly laid eggs did not prevent

hatching, but 10 minute exposure of the eggs killed 50% of fleas that developed to larval stage. These new findings, all of which were reported under Tab 4, indicated that pyriproxyfen had an unusual latent effect in which short-term exposure of flea eggs early in embryogenesis was often lethal to flea larvae that hatched from the egg 3 days later. In contrast, a longer-term (2-hour) exposure of eggs to pyriproxyfen produced embryocidal effects. Thus, these data are collectively adequate to demonstrate the effectiveness of pyriproxyfen formulations of various dilutions against cat flea in egg, larval and adult stages when the subject product, which is a manufacturing use concentrate, is used to prepare end use products. Specific claims are dependent upon concentration, frequency of application and various other factors which are beyond the scope of this review and will need to be handled on an individual case-by-case basis. It will be necessary for either the registrant or their customers who purchase this product for use in formulating their own end use products to provide labeling outlining the types of claims which are applicable to their formulation(s).--RL Vern L. McFarland, IB"

MRID 45086801 as per an earlier review partially supports the ovicidal and larvacidal claims made on the proposed label of 2517-IN. The duration of claims made (9 weeks)(63 days) could not be validated from the cited study due to differences between the test protocol and desired use pattern. The registrant may include these claims, only if it is agreed that they will submit or cite confirmatory data within 12 months.

Data Submitted in Support of (S)-Methoprene Activity

MRID 46041303. Miller, T. 2003. Dose Titration of an S-Methoprene Spot-On (sic) Dogs: Final Report, Statistical Analyses and Conclusions. Unpublished study prepared in cooperation with Auburn University. 19 p.

The primary objective was to determine the dose rate of s-methoprene in a spot-on formulation that would provide one month of residual flea ovisterilant activity on dogs: Regression-correlation analyses showed that only when the dose rate was logarithmically transformed (\log_N mg/kg) was there a highly significant correlation between dose rate and duration of residual flea ovisterilant efficacy at the 90% level. The resultant regression equation predicted that a dose rate of 2.8 mg/kg provides 30 days of efficacy at 90%. The correlation between dose rate and residual efficacy at the 100% level was not statistically significant. However, flea eggs collected on day 31 from the two cats treated at the highest dose rates of 3.5 to 3.6 mg/kg were all sterile, indicating that the predicted dose rate for a 100% residual efficacy claim is near these values.

The data submitted are partially acceptable. The study dose rate (~3.5 mg/kg) and proposed dose rate (2.8 mg/kg) are consistent with the proposed label rate. The data do not fully support the desired label claim of 1 month flea ovisterilant; however, the claim is acceptable on the condition that the registrant agree to submit confirmatory data within 12 months.

ENTOMOLOGIST'S COMMENTS AND RECOMMENDATIONS:

The data submitted are marginally adequate to support the desired registrations. However, the registrant has agreed to submit or cite confirmatory data within 12 months to verify the conclusions drawn from an amalgamation of data on Cyphenothrin, Pyriproxyfen, and (S)-Methoprene. In the interim, the data are adequate to support the following claims:

EPA Reg. Nos. 2517-IL, 2517-IN, & 2517-ON
[[Kills][Controls][Repels]] [[Fleas][Ticks]] for up to [[28 days][4 weeks]][1 month]]

EPA Reg. No. 2517-IN
Kills [flea eggs][flea larvae] for up to [63 days][9 weeks].

EPA Reg. No. 2517-ON
Kills [flea eggs] for up to [24 days][4 weeks][1 month].

Additional comments are provided on the individual labels attached.

Enclosure
002517-000IN.-ON 2006NOV7
2517-IL label
2517-IN label
2517-ON label

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