

US EPA ARCHIVE DOCUMENT

Product Performance Data Evaluation Review
by Kevin J. Sweeney, Entomologist, IB

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Product: Etofenprox Spot-on for Cats with Nylar

EPA Reg. No. or File Symbol: 69332-G

PM: George LaRocca, PM 13

Decision #: 337588

DP: 301243 and 301602

Insecticides(s): 55% etofenprox; 2.2% pyriproxyfen

Site: cats (dogs also requested)

Application volume: 0.7 ml for small cats 2.2lbs. to 5.0 lbs. (One applicator)
1.4 ml for large cats greater than 5 lbs. (Two 0.7 ml applicators)

Restrictions: Apply once per month but not more than once every 21 days.
Do not apply to cats less than 12 weeks of age and below 2.2 lbs.

Pests: for control of ticks, mosquitoes, and fleas. Claims of up to six months requested for the insect growth regulator effects.

Data submitted and reviewed:

MRID 46161310 Summary of Analyses of Efficacy Data to Support Label claims for an etofenprox-pyriproxyfen spot-on for use on Cats and Dogs by James Messina.

This volume is a registrant summary of the submitted efficacy data and provides an outline of conclusions regarding the performance of the subject product on dogs and cats against fleas, ticks, and mosquitoes.

MRID 46161311 Data Analyses of a Dose Titration to Determine the Relationship between Dose Rate of Etofenprox when applied as a Spot-On to Cats, and the Duration of Residual Efficacy Against Residual Flea Infestation by Thomas A. Miller.

This study determined the relationship between dose and residual efficacy against fleas based on three doses made to cats divided into groups on the basis of weight. Only shorthaired cats were

used. The study was conducted for 45 days and the cats were reinfested every seven days. The subject product was not tested. **The results indicated that a dose/residual performance time relationship could not be determined. At all doses tested (109-454mg etofenprox/kg cat) the product either failed or product performance declined significantly at three weeks post treatment.**

MRID 46161312 Efficacy-Etofenprox Spot-On (Cats, Dose Titration) by J.Pat Boyd

The formulation applied in this study was a 30% etofenprox formulation (approx 305 mg etofenprox/ml). Cat weights ranged from 1.7- 4.1 lbs. and were divided into four groups of four cats with equal representation of sexes. Three groups served as etofenprox treatments while the fourth served as an untreated control. Etofenprox applied to cats was tested against adult cat fleas.

Each of the three treatment groups received a different application rate. Group 1, with a mean cat weight of 3.79 kg, received 3.84 ml/cat (1171 mg), equivalent to 309 mg/kg ; Group 2, with a mean weight of 2.29 kg was treated with 1.86 ml/cat (568 mg), equivalent to 248 mg/kg while Group 3, with a mean weight of 2.76 kg received 1.16 ml/cat (354mg -near the proposed label dose), equivalent to 128 mg/kg. Cats were treated on Day 0, infested with 100 fleas on Day 1 and reinfested every 7 days thereafter for up to 45 days post treatment. Flea counts were made 1 day (24 hrs.) and 3 days (72 hrs.) after each infestation. Untreated cats had a mean weight of about 3.0 kg. There was no positive control.

Results were collected 48 hours after each infestation took place. **All three treatments failed by day 23 and showed inconsistent effectiveness thereafter. Group 3 was discontinued after day 23. Group 1 did appear to have some efficacy past day 30.**

MRID 46161313 Data Analysis of the Results of A Study on Cats to Determine the Residual Efficacy of an Etofenprox Spot-On Against Fleas and Ticks compared with Imidacloprid (Advantage) Against Fleas by Thomas Miller.

The study consisted of three treatments: an untreated control; a 9.1% imidacloprid (Advantage product) application as a positive control; and a 60.7% etofenprox formulation. There were six cats in each treatment. The untreated control had an average cat weight of 4.8 kg (10.5 lbs); the imidacloprid control had an average weight of 4.5 kg (9.9 lbs.); and the etofenprox treatment had an average weight of 3.0 kg (6.6 lbs.). The cats in the untreated control did not receive any treatment; the imidacloprid treated cats received a 0.80ml product treatment, equivalent to a mean treatment of 17.4 mg/kg; while the etofenprox treated cats received 2.0 ml (1244 mg etofenprox) each, equivalent to an average treatment of 427 mg/kg for each cat.

In this experiment, **etofenprox provided 30 days efficacy against fleas** and the statistical analysis showed that etofenprox performed as well as Advantage in these tests.

Etofenprox spot-on was also evaluated against Brown Dog ticks using the same treatment regime. It is unclear why the study director selected this species for evaluation since it strongly prefers to feed on dog hosts. This may help to explain the lack of ticks on cats in the untreated controls although cat self-grooming behavior may have also contributed to the removal of ticks. **Due to the lack of tick infestation on negative control subjects, the tick data are not acceptable.**

MRID 46161314 Efficacy - Etofenprox Spot-on (Fleas, Ticks, and Cats) by J. Pat Boyd.

The study consisted of four treatments; untreated control; 9.1% imidacloprid (Advantage product) application of 0.4 ml to 0.8 ml (17.4 mg) as a positive control; a 60.0% etofenprox formulation applied at 2.0 ml/cat; and a 60.0% etofenprox formulation applied at 2.5 ml to 4.0 ml per cat. There were six cats in each treatment. Group 1, the untreated control had an average cat weight of 5.36 kg. Group 2, the Advantage treated group, had an average cat weight of 4.28 kg. Group 3, the 2.0 ml etofenprox treatment, had an average weight of 2.96 kg while Group 4, the 3.3 ml etofenprox-treated group, had an average cat weight of 4.02 kg. Treatments were made at Day 0 and the cat was infested with 100 adult cat fleas every 7 days thereafter. Cats were infested with 50 adult American dog ticks on Day 13, 20, 27, and 35. The study was terminated at Day 38. The second group of etofenprox treated cats was evaluated 30 days after the original study because there was a 20% under-dosing error. The target dose was 1150 mg per cat.

The results indicate that **etofenprox provided control of fleas for 21-30 to 30 days** with efficacy that was equivalent to Advantage. On the other hand, ticks did not remain or attach to the negative control cats resulting in an **invalid test result that does not support a tick claim on cats**. No treated cat hair data were evaluated.

MRID 46161315 Efficacy Evaluation of an Etofenprox Squeeze-On, with Registered Positive Control Product Advantage, against Adult Cat Fleas (*Ctenocephalides felis*), Adult Brown Dog Ticks (*Rhipicephalus sanguineus* and *Dermacentor variabilis*), Nymphal Deer Ticks (*Ixodes scapularis*) and Adult *Aedes albopictus* and *Culex quinquefasciatus* Mosquitoes on cats by Marvin Sharp.

This study evaluated a 56% etofenprox formulation as a cat spot-on at two dose rates - 220 or 330 mg/kg. A Hartz d-phenothrin-based product was used as the positive control. There were four groups of five cats each. Group A was the untreated control with a mean cat weight of 3.2 kg. Group B was an etofenprox treatment with a mean cat weight of 3.3 kg. In Group B, the mean volume applied to each cat was 1.38 ml (approx. 773 mg) in order to deliver an average dose of 222 mg/kg. Group C was also an etofenprox treatment with a mean cat weight of 3.3 kg. The mean volume applied to each cat in Group C was 2.06 ml (approx 1154 mg), equivalent to a dose of 331mg etofenprox/kg. In the positive control, one ml of the Hartz product was applied according to label directions to each cat to deliver a mean dose to 241 mg d-phenothrin/kg. Cat weight in the positive control averaged 3.8 kg.

The efficacy of etofenprox was evaluated against the adult cat flea; Brown dog tick; American dog tick on day 13 infestation only; blacklegged tick - *Ixodes scapularis* nymphs in a treated hair bioassay; the Asian Tiger mosquito and the Southern House mosquito.

Results

Fleas - when applied at 1.4 ml or 2.0 ml, the product failed at 21 days.

Brown dog ticks and American Dog ticks - *in vivo*, the untreated control treatment had too few ticks and the tick test is unacceptable. In addition, the study never states how many ticks were applied to each cat.

Ixodes scapularis - the *in vitro* assay appears to be successful for the 2.0 ml dose only (1150 mg/animal with a mean dose of 331 mg/kg). However, the data tables were not labeled correctly. Both tables are labeled "Day 11". I assume that Table 5.1 is the Day 11 evaluation while Table 5.2 is the Day 28 or Day 33 evaluation.

Mosquitoes - the first evaluation was made on Day 14 with the Asian Tiger mosquito only. Since this test was successful, the second tests were conducted with the Asian Tiger mosquito and the Southern House mosquito on Day 33 and Day 29, respectively. The 2.0 ml dose performed better than the 1.4 ml dose, but both were acceptable. Between 40 and 53% of the untreated control mosquitoes fed on cat blood during the same test period. Efficacy against mosquitoes was measured on the basis of blood feeding by comparing the untreated controls to the treatments.

MRID 46161316 Dose Titration to Determine the Relationship when Applied as a Spot-on to Kittens and the Duration of Residual Flea Ovisterilization by Byron Blagburn.

This titration study resulted in a regression with a very strong correlation ($r^2 > .85$) at a high level of statistical significance. Cats, not kittens, were used as test subjects.

The product has about 22.1 mg pyriproxyfen/ml, equivalent to 15.5 mg/0.7ml dose and 31 mg/1.4 ml dose. Therefore, a 2.2 lbs. cat would receive 15.5 mg/kg and a 4.4 lbs. cat would receive 15.5 mg/kg. If we derive efficacy from the data submitted in this study and the corresponding dose relationship, a conservative estimate for efficacy is 110 days = 3-4 months for the IGR effects. Higher cat weights would receive a lower dose/kg. For instance, a 7 kg cat would receive only 4.42 mg/kg, equivalent to about 70 days control. Larger cats would be expected to receive an even smaller dose per kg.

MRID 46161317 Data Analysis of a Dose Titration to Determine the Relationship between Dose Rate of Etofenprox, when Applied as a Spot-On to Dogs, and the Duration of Residual Efficacy Against Flea and Tick Reinfestation by Thomas Miller.

This study did not reveal a dose-residual control relationship. **Cat fleas and Brown dog ticks on dogs** were evaluated against the subject product. Based on the actual experimental results presented in the study, the product appears to be efficacious for at least 3 weeks. Two application volumes were evaluated, 4.2 ml and 8.4 ml. **The application volume of 8.4 ml (4877 mg)(403 mg/kg) provided up to 30 days protection, while a 4.2 ml (2438 mg) (184 mg/kg) application provided 23 days success.** The applications were also evaluated on a weight/weight basis. The author proposes a 250 mg/kg dose as adequate but the data simply don't support this conclusion. The label also proposes a much lower application volume and I believe that such low volumes may be inadequate to treat an animal the size of "toy dog" (less than 15 lbs.) as listed on the label. Note that in this study a 60% etofenprox spot-on was applied.

MRID 46214201 Efficacy-Etofenprox Spot-on (Titration/Fleas/Ticks/Dogs) by J. Pat Boyd

This study is similar to MRID 46161317 and a 60% etofenprox spot-on was also used. Two application volumes were evaluated, 4.2 ml and 8.4 ml. **For fleas, the application volume of 8.4 ml (4877 mg)(350 mg/kg) provided up to 30 days protection, while a 4.2 ml (2438 mg) (173 mg/kg) application provided 21 days success. For ticks, both application volumes failed at 23 days. Lower volume applications were not tested.**

MRID 46161319 Efficacy Evaluation of Four Flea Products on Cats by David Young.

The study compared four products, three registered cat spot-ons and the subject product. The mean cat weight in the study was 3.7 kg = 8.14 lbs. In this test, the subject product when applied at 400 mg/kg (1480 mg or 2.68 ml/cat) was efficacious for up to 21 days against fleas. The Merial product, FrontLine Top-Spot for cats (9.7% fipronil), was efficacious for 30 days. The Hartz product, "Advanced Flea Care Flea and Tick Drops for Cats and Kittens (85.7% d-phenothrin) and Farnam product, Gentle Touch Flea Drops (7% lauryl sulfate and 5% citric acid), performed had a lower level of product performance than the etofenprox spot-on.

The average application in this study was 2.68 ml based on a 400mg/kg treatment to cats weighing 3.7 kg on average. However, the product label directs the applicator to apply 1.4 ml (775mg) to the same size cat. This dose is equivalent to 209mg/kg, one-half of the dose applied in this study where only 3-4 weeks control was shown.

Discussion

Etofenprox Application Rates: the original labeling for this product proposed a much higher dose, almost three times the dose proposed on the pending label with a wider range of cat weights. The submitted titration studies infer (but do not prove) that etofenprox might be successful at lower doses. Other submitted studies were conducted at a variety of low doses, and when compared to negative and positive control data, they show that w/w dosing of 400 mg/kg is

needed to satisfy EPA 810.3300 guideline recommendations (Note: one ml of product contains 553 mg of etofenprox).

The label dose as it is proposed would barely treat small cats with adequate etofenprox. Larger animals would receive a dose (w/w application) that is probably not adequate to kill and control pests. Based on the submitted data, volumetric doses of 2.0 ml and greater were consistently efficacious (compared to the label doses of 0.7 ml and 1.4 ml). A dose of 330-400 mg/kg is needed to control fleas for 21 days or more. The target dose of etofenprox for cats is 387 mg/kg when applied according to the label to cats weighing 2.2 lbs. However, for larger cats - say 3 kg (6.6 lbs.) - the w/w dose is less, $774 \text{ mg} / 3 \text{ kg} = 258 \text{ mg/kg}$. This latter dose was marginal in the efficacy trials and the product probably should be reapplied every three weeks for larger animals and the volume of product increased. This recommendation is supported by data from MRID 46161319 where a dose of 400 mg/kg provided three weeks control. If the same size cat used as a test subject in MRID 46161319 (avg. weight = 3.7 kg. = 8.14 lbs.) received the proposed label directed treatment of just 1.4 ml, the dose applied would equal only 209 mg/kg ($774 \text{ mg} / 3.7 \text{ g}$) or approximately $\frac{1}{2}$ of the needed dose. The data don't support this low a dose on a w/w basis and I note that nearly all of the efficacy data were generated based on weight to weight applications instead of by following the label directions and applying the product to a variety of cat subjects at the directed volume. If it were not for animal safety concerns, I would suggest 1.4 ml for cats 2.2 - 4.5 lbs. and 2.1 ml for cats 4.5 lbs. - 6.5 lbs. A higher application volume for cats weighing more than 6.5 lbs. is probably needed.

Entomologist's Recommendations

1. A re-application interval of every 21 days is recommended or an increase in product application volume. However, the animal safety study results for cats show that the proposed label application rate is at the limit of safety for cat exposure to a spot-on containing etofenprox. Therefore, EPA recommends a reapplication interval based on animal safety of 30 days. Remove the 21-day reapplication interval from the label.
2. Remove all references to dogs from the label. The animal safety study for dogs must be reviewed and accepted before dog claims can be considered for this product. Regarding the efficacy testing data on dogs, the submitted data support tick and flea control claims up to three weeks if the product label reflects the doses used in these studies. The titration studies were inconclusive. Dog studies need to be conducted in accordance with the label directions against adult cat fleas, larval cat fleas and eggs, adult Brown dog ticks, adult American dog tick, nymphal *Ixodes* ticks, *Aedes albopictus* and *Culex quinquefasciatus* or *Cx. tarsalis* mosquitoes.
3. Kills and controls adult fleas for 30 days is acceptable. Claims of repellency are unacceptable for fleas.
4. Flea egg and larval kill and control claims are acceptable.

The data support a control claim of “up to three months” based on the submitted data. However, if the product is reapplied every 30 days, what is the significance of a claim longer than 30 days?

5. The general tick kills, repels, and control claims are unacceptable for cats and should be removed from the label. The selection of the Brown dog tick as the test species was not the best choice for when testing on cats. Brown Dog ticks, a prolific breeder that can be readily available for laboratory testing, is known to strongly prefer dog hosts, especially in the adult life stage. Cat grooming behavior combined with the Brown Dog tick infestation on cats affected the outcomes of the in-vivo study. On the other hand, use of clipped hair from treated cats provided more consistent results, especially at 48 hours post-exposure with *Ixodes scapularis* ticks. The submitted *Ixodes* nymphal data are acceptable, however, they alone do not support a general tick claim.

For a tick control claim on cats to be considered, the registrant should provide additional *in vivo* study data on cats and *in vitro* data with clipped hair removed from treated and untreated cats against Lone Star ticks and American dog ticks at a minimum. Only the label rate treatment should be tested because this is the rate that will be applied. The number of replicates should be at least five for the treatment.

6. Mosquito repellency claims are acceptable for up to 30 days (1 month) based on the lack of mosquito feeding by *Aedes albopictus* and *Culex quinquefasciatus*. Kill and control claims are not acceptable.

7. Specific Label Claims:

Page 1

Front Panel:

“Flea, *Deer or Blacklegged* Tick, and Mosquito Control for Cats.” **Acceptable if the italicized phrase is added.**

Remove “Flea, Tick, and Mosquito Control for Dogs and the bracketed dog related statements.

One Application:

Breaks Flea Life Cycle for up to 3 months (90 days) - **Acceptable**

Kills and Repels Adult Fleas for up to 28 days (4 weeks) (1 month) (per application) - **Acceptable with strikeout for “Repels”.**

Kills Flea Eggs and Larvae for up to 3 months (90 days) (per application) **Acceptable**

Kills Fleas, ~~Ticks, Mosquitoes~~, Flea Eggs and Larvae - **Acceptable with strikeout of ticks and mosquitoes.**

Monthly Flea, ~~Tick~~, Mosquito, and Flea Egg Protection Acceptable with strikeout of ticks.

~~"5 in 1" Protection~~ Not acceptable. Remove from label.

Kills Fleas, ~~Ticks~~, and Mosquitoes for up to (4 weeks) (1 month) (28 days) (per application) **Acceptable with strikeout for ticks.**

Kills Flea Eggs, and Larvae for up to (3 months) (90 days) (per application) **Acceptable**

Prevents Flea Eggs and Larvae from Developing into Biting Adults for up to 90 Days (3 months) (per application) **Acceptable.**

Remove "Kills and Repels Ticks for up to 28 days (4 weeks) (1 month) (per application)" This claim is not acceptable.

"Kills Ticks [before they can] [That] Transmit Lyme Disease, for up to (4 weeks) (1 month) (per application)" is **acceptable provided another tick study as described above is submitted.**

Remove "Kills Ticks [before they can] [That] Transmit Cytauxzoonosis Disease, for up to (4 weeks) (1 month) (per application)"

Prevents Mosquitoes that Transmit West Nile Virus from Feeding on Cats for up to one month (per application) **Acceptable.**

Remove "Prevents Mosquitoes that Transmit West Nile Virus from Feeding on Dogs for up to one month (per application)."

Remove "Formulated Especially for Toy Breed Dogs [Dogs weighing less than 15 lbs.]"

Remove extended claims for [Two applications] and [Three applications] of the product as they can be misleading.

Page 2 - OK

Page 3 - Remove "Repeat applications may be necessary, but do not apply more often than once every 21 days."

Add: "Use only on Cats."

Add: "Do not Repeat Treatment to cats for 30 days."

Remove directions for use on dogs.