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444333-06

Versar inc.

# MEMORANDUM

**TO:** Jeff Evans

cc: 3770.101
J. Leahy
A. Nielsen
L. Phillips

**FROM:** Hai-Ming Chou

**DATE:** April 30, 1998

**SUBJECT:** Review of two Dislodgeable Residue Studies - the "Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Dogs (MRID # 444333-06)", and the "Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Cats (MRID # 444333-07)"

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Two Dislodgeable Residue Studies - the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Dogs (MRID # 444333-06), and the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Cats" (MRID # 444333-07) was submitted in support of the registration requirements for the pesticide Frontline® formulated as Frontline® Spray Treatment. No guideline is currently available addressing pet dislodgeable residue studies. However, compliance with Section 132 of Subdivision K (Exposure: Reentry Protection) of the Pesticide Assessment Guidelines and Series 875 Occupational and Residential Exposure Test Guidelines was used for evaluating these studies.

The following information could be used to identify the two Studies:

| | |
|---|---|
| Title: | Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Dogs |
| Sponsor: | Merial<br>Laboratorie de Toulouse<br>4 chemin du Calquet<br>Toulouse Cedex, France |
| Performing Laboratory: | Covance Laboratories Inc.<br>3301 Kinsman Boulevard<br>Madison, Wisconsin 53704 |
| Authors: | Donald L. Hughes |
| Report Dates: | November 3, 1997 |
| Identifying Codes: | MRID # 444333-06 |

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| | |
|---|---|
| Title: | Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Cats |
| Sponsor: | Merial<br>Laboratorie de Toulouse<br>4 chemin du Calquet<br>Toulouse Cedex, France |
| Performing Laboratory: | Covance Laboratories Inc.<br>3301 Kinsman Boulevard<br>Madison, Wisconsin 53704 |
| Authors: | Donald L. Hughes |
| Report Dates: | October 30, 1997 |
| Identifying Codes: | MRID # 444333-07 |

## EXECUTIVE SUMMARY

Two post-application studies, the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Dogs" (herein referred to as "the Dog Study"), and the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Cats" (herein referred to as "the Cat Study"), were conducted to examine dislodgeable residues of fipronil, the active ingredient of Frontline®, on the hair coats of dogs and cats, respectively, following their treatment with the pesticide.

Two groups of female dogs (five long-haired, and five short-haired) weighing 9.5 to 19.2 kg were included in the Dog Study, and five female cats weighing 2.8 to 3.5 kg were included in the Cat Study. Dogs and cats were topically treated on July 3, and July 1 of 1997, respectively with the Frontline® spray treatment. Each one of them received one treatment on Day 1 with the maximum label rate of 6 mL of product per kg of body weight.

Dye free 100 percent cotton gloves were used for collecting residues at the following sampling time intervals: before dosing; 2, 4, and 12 hours after dosing; and 2, 3, 5, 8, 15, 22, and 29 days after dosing. By wearing one of the gloves over the dominant hand, the sampler (the one performing the sampling) stroked with uniform medium pressure the specified body surface of the test animals. A total of five strokes were applied to each dog and a total of four strokes were applied to each cat to cover the whole body surface at each sampling interval. One glove was used for each test animal at each of the sampling intervals.

The residue levels of fipronil and its degradates (M&B46136, M&B45950, and M&B46513) in each glove were reported and used for calculating the percent of dislodgeable residues. The percent of dislodgeable residues was calculated based on the total residues levels of fipronil and its degradates (M&B46136, M&B45950, and M&B46513) divided by the actual amount of fipronil sprayed for each treatment.

At least one laboratory control and two laboratory fortification (recovery) samples were analyzed along with each analytical set. One fortified sample was analyzed at the limit of quantification (LOQ), and one at or above the highest level of residues found in the field samples. Most of the laboratory recoveries for both studies fell within the range of 70 percent to 120 percent (see "Appendix" of this review).

The half life was calculated as 6.12 days (r=0.986) based on the results from the short-hair dogs, and 5.27 days (r=0.992) based on the long-hair dogs. The half life was 4.63 days (r=0.885) based on the results from the cats.

Regression analysis and data analysis were conducted by Versar to examine the dissipation data. Coefficients of variability (CV) for both studies were large suggesting considerable variability among residue levels on the test animals.

Coefficients of correlation ranged from 0.885 to 0.992. R square values ranged from 0.782 to 0.984. These results along with considerably small *p*-values for F statistics indicated, in general, good regression model and their ability to predict residue levels.

In summary, both of the Dislodgeable Residue Studies only partially met the criteria contained in Subdivision K of the Pesticide Assessment Guidelines. Several aspects of the sampling design and the variability of the results need to be further examined, as described in the "Review Summary" and "Comments" sections of this review. For example:

- Tox. data not provided so re-entry interval could not be determined.
- Storage stability, field controls, and field recovery were not examined.
- Method validation study was conducted, but no results or method description were provided.

## Study Background

Frontline® is a new pesticide used to control fleas and ticks on dogs and cats. Two post-application studies, the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Dogs" (herein referred to as "the Dog Study"), and the "Dislodgeable Residues of Fipronil Following Application of Frontline Spray Treatment to Cats" (herein referred to as "the Cat Study"), were conducted to examine dislodgeable residues of fipronil, the active ingredient of Frontline®, on the hair coats of dogs and cats, respectively, following their treatment with the pesticide.

## Materials

A liquid formulation, known as Frontline® Spray Treatment, was used in both studies. It was packaged in 250 mL HDPE (High Density Polyethylene) containers with spray nozzles containing 0.29 percent (w/w) of active ingredient (ai), fipronil. Each container used in the Dog Study contained approximately 250 mL of the product, and each full trigger pump depression delivered approximately 1.5 mL of the product. In the Cat Study, 100 mL of the product was contained in the containers, and 0.5 mL of the product was delivered per full trigger pump depression. The purity of the reference standards of the ai and its degradates (M&B46136, M&B45950, and M&B46513) was documented and certificates of analysis attached.

## Test Animals and Housing

Two groups of female dogs (five long-haired mixed-bred dogs supplied by LBL Kennels, and five short-haired purebred beagles supplied by Covance Research Products, Inc.) weighing 9.5 to 19.2 kg were included in the Dog Study, and five female mixed-bred cats (supplied by Liberty Research, New York) weighing 2.8 to 3.5 kg were included in the Cat Study. All the animals were vaccinated and dewormed prior to study initiation. Dogs displaying signs of skin diseases or receiving concomitant medication other than commercially available heartworm preventative were excluded. All the animals entered the study for acclimation at least ten days before treatment (except one dog) and were observed once daily (twice daily for mortality and moribundity) throughout the acclimation, treatment, and sampling periods. Body weights of the animals were measured weekly prior to treatment, on Day 1 prior to treatment, and weekly thereafter. All the dogs were bathed before treatment.

Dogs were provided *ad libitum* with Certified Canine Diet #5007 (PMI Feeds, Inc.) which was routinely analyzed for nutritional components and environmental contaminants. Cats were provided *ad libitum* with Laboratory Feline Diet #5003 (PMI Feeds, Inc.). Water was also provided *ad libitum* and was routinely analyzed for specified microorganisms and environmental contaminants. The results indicated there were no known contaminants in the diet or water at levels that might interfere with the studies.

All the pets were caged in individual cages, and the dog were exercised individually. The animals rooms were environmentally controlled with the temperature (18°C to 29°C), the relative humidity (50 percent ± 20 percent), and a 12 hour light/12 hour dark cycle.



5

## Application and Sampling

Dogs and cats were topically treated on July 3, and July 1 of 1997, respectively with the Frontline® spray treatment. Each one of them received one treatment on Day 1 with the maximum label rate of 6 mL of product per kg of body weight (see "Comments" below). After each treatment, the table used for treatment was wiped down with 70 percent isopropyl alcohol to dry. To prevent cross-contamination among animals, new disposable surgical gowns and latex gloves were worn by personnel for each pet being treated.

Dye free 100 percent cotton gloves (supplied by Guerin, 70 rue Tolstoï, 69100 Villeurbanne. France - ref.: 380001) were used for collecting residues at the following sampling intervals: before dosing; 2, 4, and 12 hours after dosing; and 2, 3, 5, 8, 15, 22, and 29 days after dosing. These gloves covered the wrist area on the hand and were placed in sealed containers prior to use. By wearing one of the gloves over the dominant hand, the sampler (the one performing the sampling) stroked with uniform medium pressure the specified body surface using motions that ran with the lay of the haircoat. A total of five strokes were applied to each of the dogs to cover the whole body surface beginning from the head and ending at the tail surface (one stroke on the back, one stoke each on the right and left flanks, and one stoke each over the left and right ventral zones), while a total of four strokes were to each of the cats (one stoke on the back, one stoke each on the right and left flanks, and one stoke over the ventral zone). One glove was used for each pet at each of the sampling intervals.

## Sample Storage and Handling

Each sample was coded (refer to p. 20 of the Dog Study Report, and p. 18 of the Cat Study Report). After sampling, gloves were and removed and placed into pre-labeled glass containers capped with Teflon®-lined lids. All samples were stored frozen prior to analysis.

## Analytical Method and QA/QC

A method validation study was conducted prior to sample analysis; however, the method description and the results of the method validation study were not provided in the Study Report (see "Comments" below). Each entire glove was extracted and analyzed using the validated method. The residue levels of fipronil and its degradates (M&B46136, M&B45950, and M&B46513) in each glove were reported and used for calculating the percentage of dislodgeable residues. The percentage of dislodgeable residues was calculated based on the total residues levels of fipronil and its degradates (M&B46136, M&B45950, and M&B46513) divided by the actual amount of fipronil sprayed for each treatment (see "Appendix" for calculations). Half of the LOQ (3.00 µg/glove) value was used for calculation when the amount of fipronil and its degradates were less than the LOQ.

At least one laboratory control and two laboratory fortification (recovery) samples were analyzed along with each analytical set (see "Comments" below). Fortifications covered the range of residues found in the field samples. One fortified sample was analyzed at the limit of quantification (LOQ), and one at or above the highest level of residues found in the field samples.



6

**Data Summary**

The average dislodgeable residue levels for the two studies were summarized in Table 1, 2, and 3. Summaries of dislodgeable residue levels on each test animal were reported on p. 34 - p. 43 of the Dog Study Report, and p. 28 - 32 of the Cat Study Report. The highest average dislodgeable residue level (0.886 percent) and the highest individual dislodgeable residue level (1.45 percent) were both obtained 12 hours after treatment within the group of short-haired dogs (Table 1). The highest average dislodgeable residue level (0.688 percent) and the highest individual dislodgeable residue level (0.883 percent) were both obtained 4 hours after treatment within the group of long-haired dogs (Table 2). For the Cat Study, the highest average dislodgeable residue level (0.443 percent) was obtained 4 hours after treatment, and the highest individual dislodgeable residue level (0.592 percent) obtained 12 hours after treatment (Table 3). Residues of the degradate, M&B46513, were not detected in either study (see "Comments").

Most of the laboratory recoveries for both studies fell within the range of 70 percent to 120 percent (see "Appendix" of this review). One recovery in the Dog Study was high, and three recoveries in the Cat Study were outside this range (one slightly high and two low). Mean recoveries of fipronil and its metabolites were between 98 and 107 percent.

The average dislodgeable residue levels were analyzed by Versar using the linear regression approach. Each of the average dislodgeable residue levels (percent) were natural-log transformed. Linear correlation coefficients, slopes, and intercepts are presented in Table 4, 5, and 6. Figure 1 to 6 present predicted dissipation curves for both studies with reported data points (both natural-log transformed), and residual plots of predicted dissipation data versus reported data (both natural-log transformed). In addition, half-life values and the summary of regression analysis results are presented in Table 7. Table 8 summarizes predicted dislodgeable residue levels without natural-log transformation.

**Data Analysis**

Coefficients of variability (CV) for both studies were calculated by Versar and were presented in Tables 1, 2, and 3. Each CV, calculated based on the percent of dislodgeable residues at each sampling interval, indicated the variability among test animals. The CVs among the short-haired dogs ranged from 28.0 to 53.0, while the CVs among the long-haired dogs ranged from 15.7 to 59.1. The CVs among the cats ranged from 7.44 to 78.3. These results suggest considerable variability among test animals.

The half life was calculated as 6.12 days (r=0.986) based on the results from the short-hair dogs, and 5.27 days (r=0.992) based on the long-hair dogs. The half life was 4.63 days (r=0.885) based on the results from the cats.

Based on the results of regression analysis (Table 4, 5, 6, and 8), coefficients of correlation were 0.986 (short-hair dogs), 0.992 (long-hair dogs), and 0.885 (cats). R square values for each regression model were 0.971 (short-hair dogs), 0.984 (long-hair dogs), and 0.782 (cats). These results along with considerably small *p*-values for F statistics indicated, in general, good regression models and their ability to predict residue levels. The relatively poor correlation

and the low R square value of the dissipation data from the Cat Study might be partially explained by the high percentage of less-than-LOQ residue values obtained from the Study, in particular those obtained on Day 15, 22, and 20 after treatment. The use of one-half LOQ value to represent less-than-LOQ for calculating residue levels may have brought in additional variability.

**Review Summary**

No guideline is currently available addressing pet dislodgeable residue studies. However, compliance with Section 132 of Subdivision K (Exposure: Reentry Protection) of the Pesticide Assessment Guidelines and Series 875 Occupational and Residential Exposure Test Guidelines were used for evaluating these studies. The itemized checklist below describes the major technical aspects of Subdivision K and is based on the "Checklist for Residue Dissipation Data" used for study review by the U.S. EPA/OPP/OREB.

- *Typical end use product of the active ingredient used.* This criterion was met as a commercial product was used and the active ingredient tested in both studies.

- *Site(s) treated representative of reasonable worst-case climatic conditions expected in intended use areas.* This criterion was not applicable to these studies. However, temperatures and relative humidities were reported in both studies.

- *End use product applied by application method recommended for the crop. Application rate given and should be at the least dilution and highest, label permitted, application rate.* This criterion was partially met. The equipment used in both studies, a ready-to-use spray pump bottles, was in conformity with the application method on the label. Based on the label, the maximum label rate is 2 pumps/lb of body weight with approximately 1.5 mL per full depression of pump triggers, which is equivalent to 6.6 mL of product per kg of body weight. However, 6 mL of product per kg of body weight was used in both studies.

- *Application(s) occurred at time of season that the end-use product is normally applied to achieve intended pest control.* The criterion was met. Pets may be treated for fleas and ticks virtually at any time of the year. The test animals were treated in July, which is commonly accepted as one of the treatment seasons.

- *Meteorological conditions including temperature, wind speed, daily rainfall, and humidity provided for the duration of the study.* The criterion was met as temperatures and relative humidities were reported in both studies. The study was conducted indoors.

- *Reported residue dissipation data in conjunction with toxicity data must be sufficient to support the determination of a reentry interval.* This criterion was not met. Toxicity data were not provided in the study report.



8

- *Residue storage stability, method efficiency (residue recovery), and limit of quantification provided.* This criterion was partially met. A method validation study was conducted, however, no results were reported. Laboratory recovery data were collected and reported, however, storage stability and field recovery were not examined. The limit of quantification was reported as 3.00 µg/glove.

- *Duplicate foliar and/or soil samples collected at each collection period.* This criterion was met as five samples were collected at each collection period in both studies (5 short-haired dogs, 5 long-haired dogs, and 5 cats).

- *Control and baseline foliar or soil samples collected.* The criterion was partially met. A single pre-treatment sample was collected on each test animal in both studies; however, no field control samples were collected.

- *Sufficient collection times to establish dissipation curve.* This criterion was met. All the samples were collected up to 29 days after treatment.

- *Foliar residue data expressed as ug or mg/cm$^2$ leaf surface area.* This criterion was not applicable to these studies. The residue data in both studies were expressed as percent of dislodgeable residues based on total residue levels of fipronil and its degradates divided by the amount of fipronil applied.

- *Soil residue data expressed as ug/g of fine soil material.* This criterion was not applicable to these studies.

**Comments**

Additional notes and data gaps critical to the scientific validity of both studies, not addressed above, are presented below. The following issues were identified:

- Coefficients of variability (CV) for both studies were large suggesting considerable variability among residue levels on the test animals. The variability might be explained by the following: (1) lack of uniformity among strokes applied by the sampler while sampling was performed (one applicator was used for treatment, however, it was not clear whether the same sampler(s) was used ). (2) variability resulting from the sampling procedures since different portions of the test animals' hair coats might be sampled, (3) variability resulting from test animals since the ability of their hair coats to retain residues might be different (also having effects on the amount of residues that could be dislodged). In addition, whether the pets were restrained between sampling intervals was not clear; their activities might have effects on the dislodgeable residue levels on the hair coats. However, it should be noted that the residue values were reported as percentages; thus, variability resulting from the actual amount of ai applied (e.g., variation from squeezing the pumps) would be minimal.

- Each sampling on each test animal at each interval used the same glove and contained four or five strokes over different areas of the hair coats. It was possible that the residues collected on the glove may be dislodged back to the hair coat among strokes.

- Whether the same portions of the hair coat on each test animal were used for sampling was not clear. The whole sampling procedure would be questionable if the same portions of the hair coats were stroked repetitively for quantifying dislodgeable residues.

- It was noted in the summaries of both Study Reports that "topical" applications were performed. However, what portions of the hair coats were treated was not described.

- Since the test animals in both studies were treated on the same day, it was possible that the pesticide residues from the previous treatments were still retained in the air and would interfere with the next treatments. The possibility of cross-contamination between treatments should be further examined in particular when no ventilation information was provided in either study.

- Dislodgeable residue levels were calculated based on total residue levels of fipronil (ai) and degrades (M&B46513, M&B45950, and M&B46136). However, the toxicological information was not provided for both the fipronil and the degradates. The rationale of including the degradates for assessing dislodgeable residues therefore should be further examined.

- It was noted by the author that all the values of the degradate, M&B46513, were below LOQ and were considered zero because the photo-product could not be formed under the design of the studies. However, the studies were not conducted in a dark room, so the possibility of forming photo-products could not be precluded.

- The length of storage periods for all the samples (from the day of sampling to the day of analysis) may be more than one month (samples were extracted and analyzed in August, 1997, while sampling was conducted in July, 1997), however, storage stability was not examined in this study.

- Field recovery data were not collected.

- At least one laboratory control and two laboratory recovery samples were analyzed with each analytical set, and one fortification sample was analyzed at the LOQ. However, the definition of an "analytical set" was not provided. In addition, not every analytical set contained a fortification sample at the LOQ (e.g., Set # 204 in the Cat Study, 60 ug/glove was used).

- The validation study results and method description were not provided for these studies. However, it was noted in the Reports that the "Covance Study No. 6848-104, Validation of an Analytical Method for the Determination of Fipronil, M&B46136, M&B45950, and M&B46513 in Dye-Free 100 percent Cotton Gloves" should be referenced. Gas chromatography (GC) with electron capture detectors was used for analyzing fipronil levels in the study "Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment", therefore, it was very likely that GC was used in the Dog Study and the Cat Study.

In summary, both of the Dislodgeable Residue Studies only partially met the criteria contained in Subdivision K of the Pesticide Assessment Guidelines. Regression analysis of the results indicated, in general, good regression models and their ability to predict residue levels. However, several aspects of the sampling design and the variability of the results need to be further examined.

Table 1. Dissipation Data, the Short-Haired Dogs

| Sampling Interval | Average Percent Dislodgeable Residue (N = 5) | Standard Deviation | Range | Coefficient of Variability (CV)* |
|---|---|---|---|---|
| 2 hr | 0.629 | 0.2063 | 0.405-0.878 | 32.8 |
| 4 hr | 0.772 | 0.2766 | 0.486-1.10 | 35.8 |
| 12 hr | 0.886 | 0.4223 | 0.469-1.45 | 47.7 |
| Day 2 | 0.687 | 0.3635 | 0.245-1.07 | 52.9 |
| Day 3 | 0.486 | 0.2461 | 0.161-0.743 | 50.6 |
| Day 5 | 0.299 | 0.1524 | 0.0704-0.420 | 51.0 |
| Day 8 | 0.208 | 0.1103 | 0.0448-0.310 | 53.0 |
| Day 15 | 0.118 | 0.0475 | 0.0354-0.149 | 40.3 |
| Day 22 | 0.0591 | 0.01657 | 0.0315-0.0745 | 28.0 |
| Day 29 | 0.0301 | 0.00920 | 0.0220-0.0448 | 30.6 |

* CV = 100 * standard deviation / average

Table 2. Dissipation Data, the Long-Haired Dogs

| Sampling Interval | Average Percent Dislodgeable Residue (N = 5) | Standard Deviation | Range | Coefficient of Variability (CV)* |
|---|---|---|---|---|
| 2 hr | 0.575 | 0.0901 | 0.454-0.702 | 15.7 |
| 4 hr | 0.688 | 0.1900 | 0.375-0.883 | 27.6 |
| 12 hr | 0.592 | 0.1389 | 0.451-0.757 | 23.5 |
| Day 2 | 0.509 | 0.2288 | 0.266-0.793 | 45.0 |
| Day 3 | 0.351 | 0.2075 | 0.138-0.685 | 59.1 |
| Day 5 | 0.275 | 0.1525 | 0.182-0.546 | 55.5 |
| Day 8 | 0.145 | 0.0841 | 0.085-0.291 | 58.0 |
| Day 15 | 0.0688 | 0.03264 | 0.0368-0.1216 | 47.4 |
| Day 22 | 0.0302 | 0.01370 | 0.0187-0.0540 | 45.4 |
| Day 29 | 0.0155 | 0.00567 | 0.0115-0.0254 | 36.6 |

* CV = 100 * standard deviation / average



17

Table 3. Dissipation Data, the Cats

| Sampling Interval | Average Percent Dislodgeable Residue (N = 5) | Standard Deviation | Range | Coefficient of Variability (CV)* |
|---|---|---|---|---|
| 2 hr | 0.337 | 0.0957 | 0.210-0.473 | 28.4 |
| 4 hr | 0.443 | 0.1394 | 0.212-0.559 | 31.5 |
| 12 hr | 0.384 | 0.1577 | 0.204-0.592 | 41.1 |
| Day 2 | 0.370 | 0.1557 | 0.176-0.567 | 42.1 |
| Day 3 | 0.156 | 0.0878 | 0.0772-0.290 | 56.3 |
| Day 5 | 0.0554 | 0.04338 | 0.0188-0.115 | 78.3 |
| Day 8 | 0.0193 | 0.01046 | 0.00862-0.0368 | 54.2 |
| Day 15 | 0.00883 | 0.000657 | 0.00816-0.00976 | 7.44 |
| Day 22 | 0.00883 | 0.000657 | 0.00816-0.00976 | 7.44 |
| Day 29 | 0.00883 | 0.000657 | 0.00816-0.00976 | 7.44 |

* CV = 100 * standard deviation / average

Table 4. Data Analysis - Fipronil Dissipation Data (Short-Haired Dogs)

SUMMARY OUTPUT

| *Regression Statistics* | |
|---|---|
| Multiple R | 0.985551696 |
| R Square | 0.971312146 |
| Adjusted R Square | 0.967726165 |
| Standard Error | 0.210295366 |
| Observations | 10 |

ANOVA

| | *df* | *SS* | *MS* | *F* | *Significance F* |
|---|---|---|---|---|---|
| Regression | 1 | 11.9787129 | 11.9787129 | 270.863664 | 1.87368E-07 |
| Residual | 8 | 0.353793129 | 0.04422414 | | |
| Total | 9 | 12.33250603 | | | |

| | *Coefficients* | *Standard Error* | *t Stat* | *P-value* | *Lower 95%* | *Upper 95%* | *Lower 95.0%* | *Upper 95.0%* |
|---|---|---|---|---|---|---|---|---|
| Intercept | -0.358910903 | 0.088448828 | -4.05783672 | 0.00364436 | -0.562874399 | -0.15494741 | -0.5628744 | -0.15494741 |
| Slope | -0.113246557 | 0.00688097 | -16.4579362 | 1.8737E-07 | -0.129114111 | -0.097379 | -0.12911411 | -0.097379 |

RESIDUAL OUTPUT

| *Days after Treatment* | *Predicted Natural Log of Residues (%)* | *Residuals* |
|---|---|---|
| 0.083 | -0.368310367 | -0.095313655 |
| 0.167 | -0.377823078 | 0.119052349 |
| 0.5 | -0.415534182 | 0.294495853 |
| 2 | -0.585404017 | 0.20998303 |
| 3 | -0.698650574 | -0.022896081 |
| 5 | -0.925143688 | -0.282168017 |
| 8 | -1.26488336 | -0.30533384 |
| 15 | -2.057609259 | -0.079461395 |
| 22 | -2.850335159 | 0.021810804 |
| 29 | -3.643061058 | 0.139830951 |

Figure 1. Dissipation of Fipronil on Short-Haired Dogs

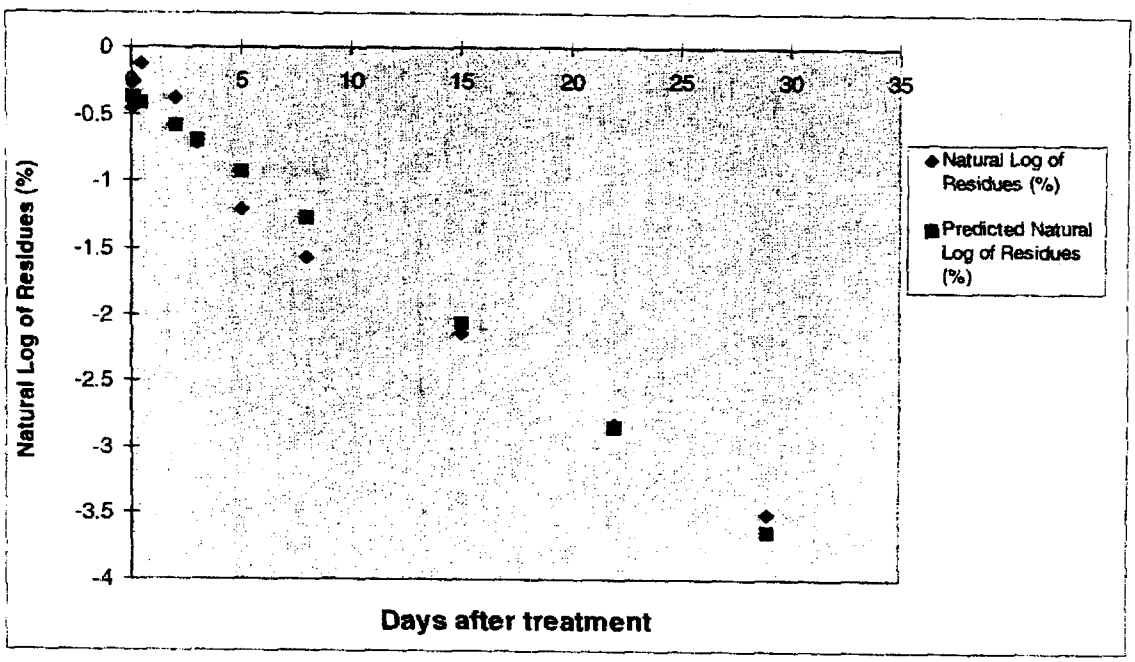
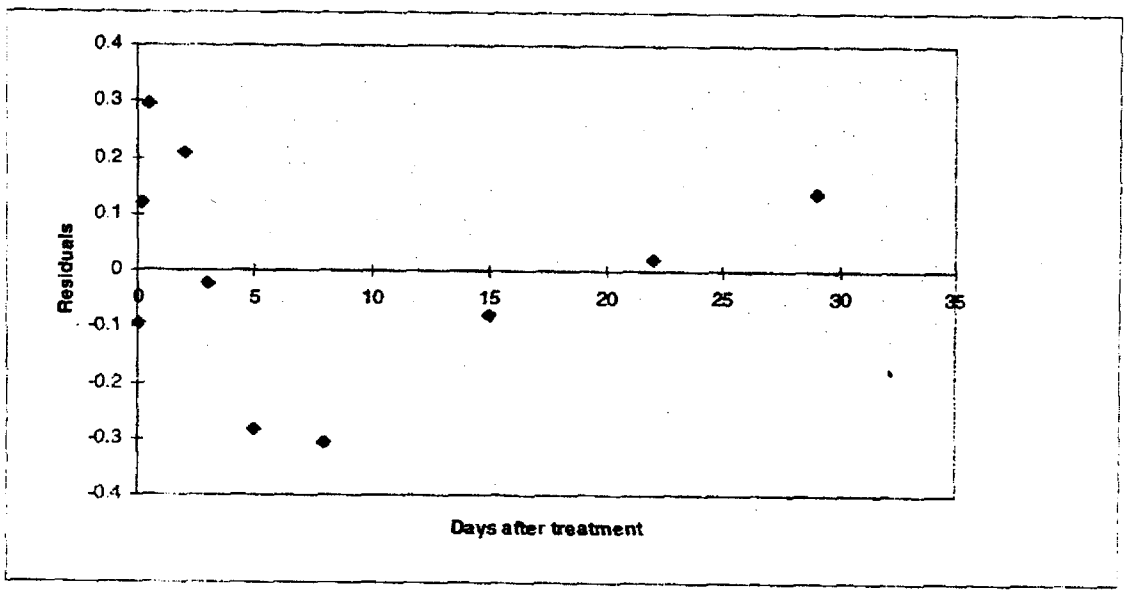



Figure 2. Residual Plot of Dissipation Data vs. Predicted Data (Short-Haired Dogs)






15

Table 5. Data Analysis - Fipronil Dissipation Data (Long-Haired Dogs)

SUMMARY OUTPUT

| *Regression Statistics* | |
|---|---|
| Multiple R | 0.99214465 |
| R Square | 0.98435101 |
| Adjusted R Square | 0.98239488 |
| Standard Error | 0.17924551 |
| Observations | 10 |

ANOVA

| | *df* | *SS* | *MS* | *F* | *Significance F* |
|---|---|---|---|---|---|
| Regression | 1 | 16.16777299 | 16.167773 | 503.215039 | 1.6502E-08 |
| Residual | 8 | 0.257031634 | 0.03212895 | | |
| Total | 9 | 16.42480463 | | | |

| | *Coefficients* | *Standard Error* | *t Stat* | *P-value* | *Lower 95%* | *Upper 95%* | *Lower 95.0%* | *Upper 95.0%* |
|---|---|---|---|---|---|---|---|---|
| Intercept | -0.55890091 | 0.075389468 | -7.41351448 | 7.52171E-05 | -0.73274945 | -0.38505237 | -0.73274945 | -0.38505237 |
| Slope | -0.13156641 | 0.005865003 | -22.432455 | 1.65021E-08 | -0.14509114 | -0.11804168 | -0.14509114 | -0.11804168 |

RESIDUAL OUTPUT

| *Days after Treatment* | *Predicted Natural Log of Residues (%)* | *Residuals* |
|---|---|---|
| 0.083 | -0.56982092 | 0.016435683 |
| 0.167 | -0.5808725 | 0.206906059 |
| 0.5 | -0.62468412 | 0.100435471 |
| 2 | -0.82203373 | 0.146726471 |
| 3 | -0.95360014 | -0.093368911 |
| 5 | -1.21673297 | -0.074251213 |
| 8 | -1.6114322 | -0.319589332 |
| 15 | -2.53239709 | -0.144154446 |
| 22 | -3.45336197 | -0.046551383 |
| 29 | -4.37432686 | 0.2074116 |

Figure 3. Dissipation of Fipronil on Long-Haired Dogs

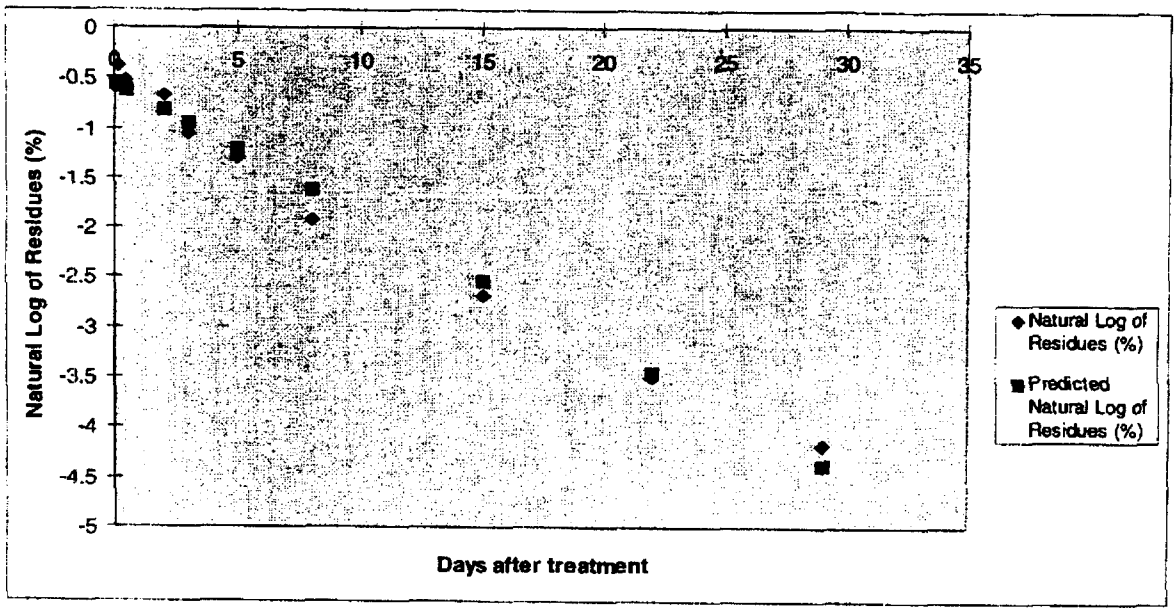
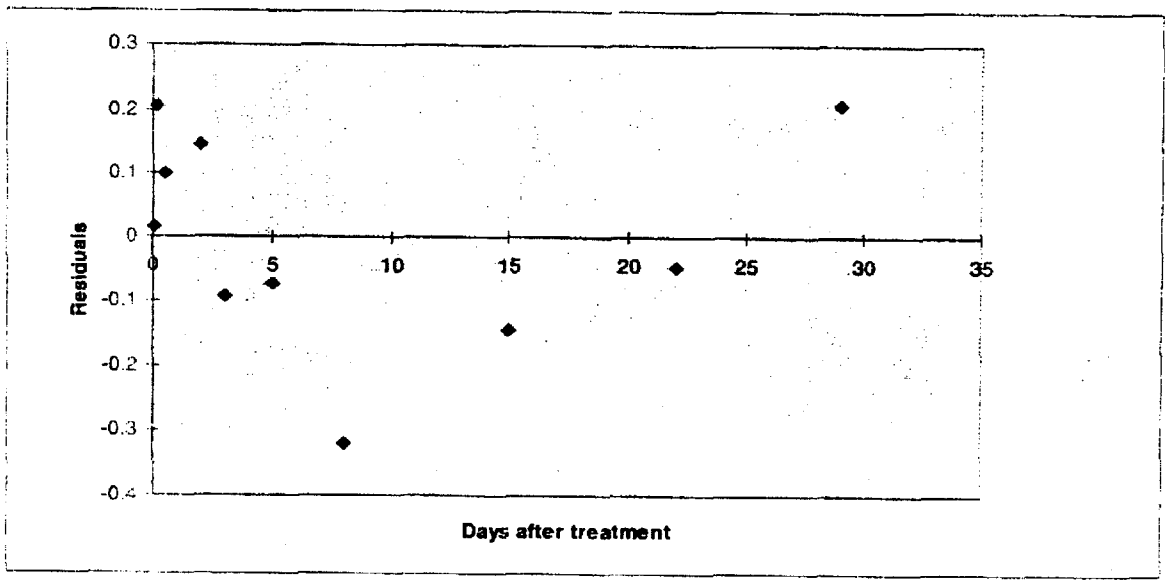



Figure 4. Residual Plot of Dissipation Data vs. Predicted Data (Long-Haired Dogs)






17

Table 6. Data Analysis - Fipronil Dissipation Data (Cats)

SUMMARY OUTPUT

| *Regression Statistics* | |
|---|---|
| Multiple R | 0.88456467 |
| R Square | 0.782454656 |
| Adjusted R Square | 0.755261488 |
| Standard Error | 0.85300428 |
| Observations | 10 |

ANOVA

| | *df* | *SS* | *MS* | *F* | *Significance F* |
|---|---|---|---|---|---|
| Regression | 1 | 20.93638973 | 20.9363897 | 28.77394264 | 0.000674323 |
| Residual | 8 | 5.820930414 | 0.7276163 | | |
| Total | 9 | 26.75732015 | | | |

| | *Coefficients* | *Standard Error* | *t Stat* | *P-value* | *Lower 95%* | *Upper 95%* | *Lower 95.0%* | *Upper 95.0%* |
|---|---|---|---|---|---|---|---|---|
| Intercept | -1.40522415 | 0.35876791 | -3.91680558 | 0.004436308 | -2.23254497 | -0.57790333 | -2.23254497 | -0.57790333 |
| Slope | -0.1497169 | 0.027910726 | -5.36413485 | 0.000674323 | -0.214079192 | -0.08535461 | -0.21407919 | -0.08535461 |

RESIDUAL OUTPUT

| *Days after Treatment* | *Predicted Natural Log of Residues (%)* | *Residuals* |
|---|---|---|
| 0.083 | -1.417650653 | 0.329978304 |
| 0.167 | -1.430226873 | 0.616041364 |
| 0.5 | -1.4800826 | 0.522969874 |
| 2 | -1.704657951 | 0.710405677 |
| 3 | -1.854374851 | -0.003524421 |
| 5 | -2.153808651 | -0.739367034 |
| 8 | -2.602959351 | -1.344690832 |
| 15 | -3.650977652 | -1.078622612 |
| 22 | -4.698995953 | -0.030604311 |
| 29 | -5.747014254 | 1.01741399 |

Figure 5. Dissipation of Fipronil on Cats

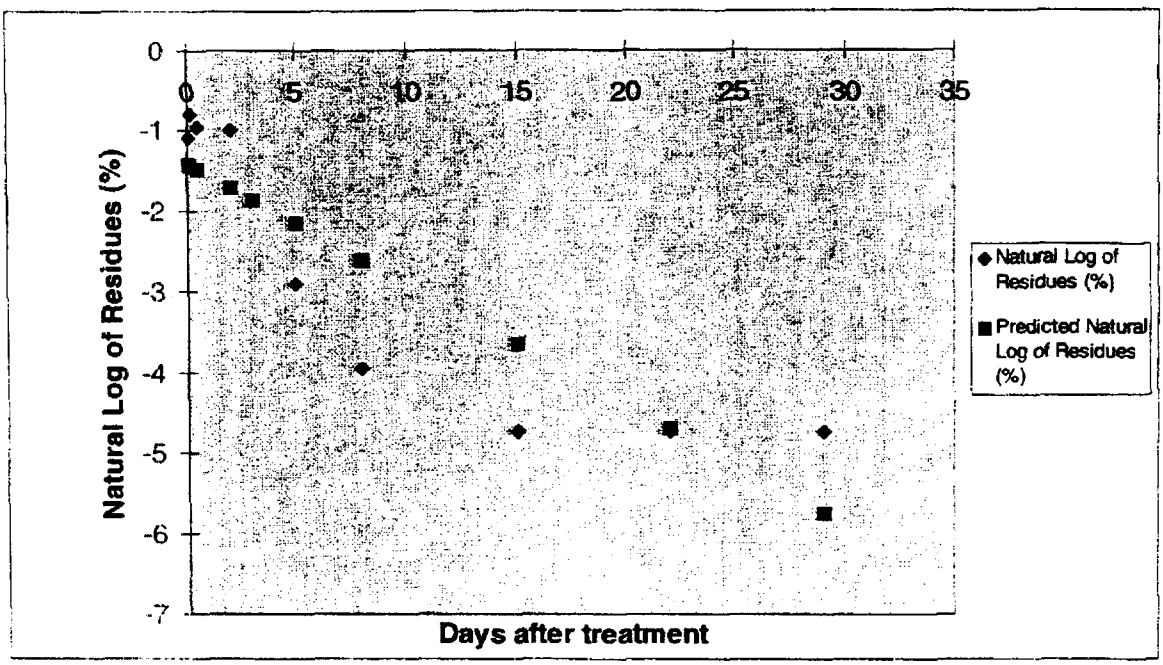
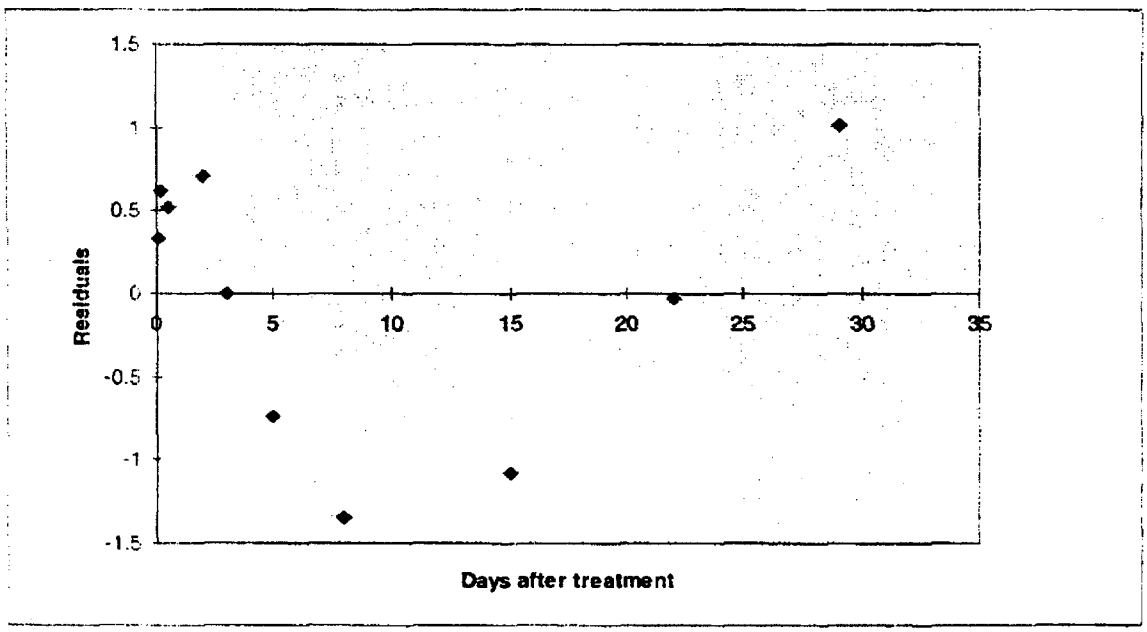



Figure 6. Residual Plot of Dissipation Data vs. Predicted Data (Cats)






19

Table 7. Summary of Regression Analysis and Half Life

| | Slope | Intercept | Correlation Coefficient | Half Life* (Days) |
|---|---|---|---|---|
| Short-Haired Dogs | -0.113 | -0.359 | 0.986 | 6.12 |
| Long-Haired Dogs | -0.132 | -0.559 | 0.992 | 5.27 |
| Cats | -0.150 | -1.410 | 0.885 | 4.63 |

* Half Life = - Ln 2 / slope

Table 8. Predicted Dislodgeable Residues (%) vs. Reported Average Dislodgeable Residues (%)

| Days after treatment | Short-Haired Dogs | | Long-Haired Dogs | | Cats | |
|---|---|---|---|---|---|---|
| | Predicted* | Reported | Predicted* | Reported | Predicted* | Reported |
| 2 hr | 0.692 | 0.629 | 0.566 | 0.575 | 0.242 | 0.337 |
| 4 hr | 0.685 | 0.772 | 0.559 | 0.688 | 0.239 | 0.443 |
| 12 hr | 0.660 | 0.886 | 0.535 | 0.592 | 0.228 | 0.384 |
| Day 2 | 0.557 | 0.687 | 0.440 | 0.509 | 0.182 | 0.370 |
| Day 3 | 0.497 | 0.486 | 0.385 | 0.351 | 0.157 | 0.156 |
| Day 5 | 0.396 | 0.299 | 0.296 | 0.275 | 0.116 | 0.0554 |
| Day 8 | 0.282 | 0.208 | 0.200 | 0.145 | 0.0741 | 0.0193 |
| Day 15 | 0.128 | 0.118 | 0.079 | 0.0688 | 0.0260 | 0.00883 |
| Day 22 | 0.0578 | 0.0591 | 0.0316 | 0.0302 | 0.00910 | 0.00883 |
| Day 29 | 0.0262 | 0.0301 | 0.0126 | 0.0155 | 0.00319 | 0.00883 |

* Predicted Percent Dislodgeable Residue (%) = $\text{Exp}^{(\text{intercept + slope x time})}$

# APPENDIX

The following items were attached in the Appendix:

- Laboratory recoveries for both studies
- Calculation (the Dog Study)
- Product label

Page _____ is not included in this copy.

Pages 23 through 27 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

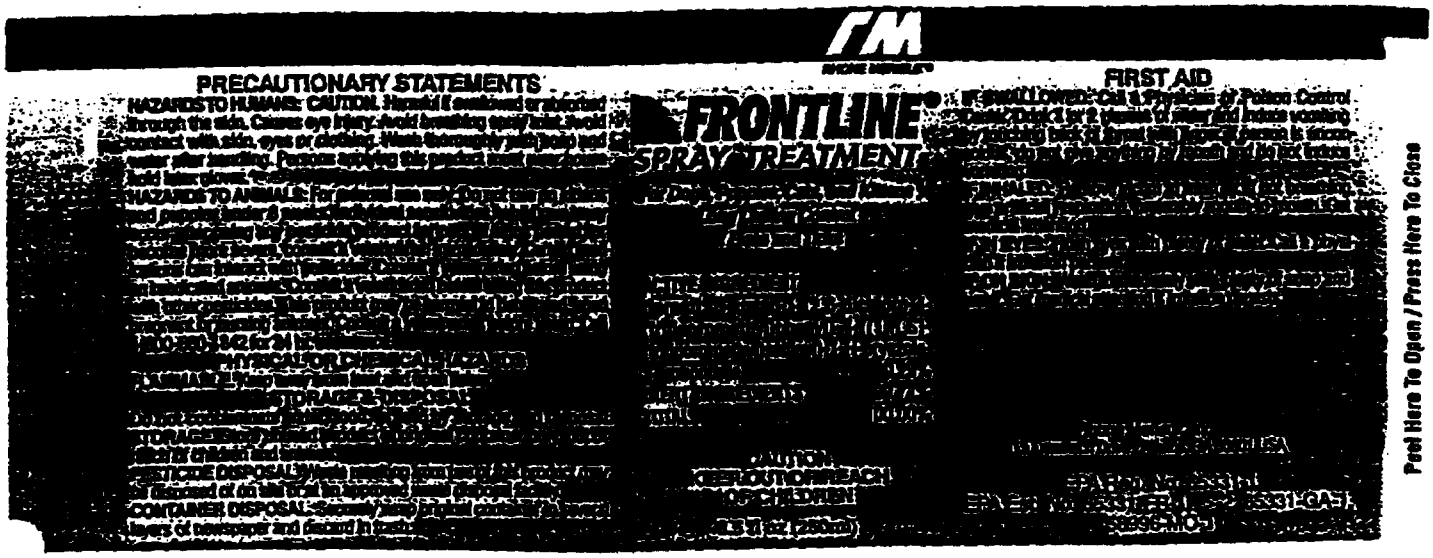
_____ The document is not responsive to the request.

_____ Internal deliberative information.

_____ Attorney-Client work product.

_____ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.




Peel Here To Open / Press Here To Close

**FRONTLINE® SPRAY TREATMENT FOR DOGS, CATS, PUPPIES, AND KITTENS**

Frontline® provides effective flea and tick control for adult dogs and cats and for puppies and kittens 8 weeks of age or older.

- Fast-acting control.
- Prevents reinfestation.
- Kills adult fleas before they lay eggs.
- Kills fleas and ticks for a minimum of 30 days.

Frontline® is the only flea control product that contains fipronil, a patented GABA inhibitor. Frontline® rapidly controls flea infestation by killing adult fleas. It quickly eliminates stress to pets from flea and tick annoyance, blood loss, biting, and flea allergies.

Frontline®'s residual activity prevents reinfesta-
· killing fleas and ticks for at least 30 days.
▲ have shown Frontline® may protect dogs against fleas for up to 90 days.

**DIRECTIONS FOR USE**

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. **TO PREVENT HARM TO YOU AND YOUR PET, READ ENTIRE LABEL AND ATTACHED DIRECTIONS BEFORE EACH USE.** Follow all directions and precautionary statements carefully. Use only on dogs and cats. Do not use on any other animals.

To kill fleas and all stages of brown dog ticks, American dog ticks, lone star ticks, and deer ticks (known to carry Lyme Disease), apply to dogs, cats, puppies or kittens as follows:

Wear household latex gloves. Hold bottle in upright position. Ruffle the animal's coat with one hand while applying spray mist to the animal's back, sides, stomach, legs, shoulders, and neck. For head and eye area, spray Frontline® on a gloved hand and rub gently into animal's hair. Do not get this product in your pet's eyes or mouth.

Apply spray mist until animal's hair is damp to thoroughly wet.

Approximately 1 to 2 pumps per pound of the animal's body weight will be required. Pets with long or dense coats will require the higher rate.

As with any flea control product wash hands and exposed skin thoroughly with soap and water after use.

To prevent flea build-up or reinfestation, use Frontline® prior to the onset of flea season and monthly thereafter. Ticks do not need to receive spray directly upon their body for complete control. Do not reapply Frontline® for 30 days.

Product performance is unaffected by exposure to moderate rainfall or by bathing with most brands of pet shampoo.

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