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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 5, 2009

MEMORANDUM

Subject:	Name of Pesticide Product:	RF 2042 [CDSO]
	EPA Reg. No. /File Symbol:	2724-TOA
	DP Barcodes	357272, 359984
	Decision No.:	399095
	Action Code:	R310
	PC Codes:	128965 (Etofenprox)
		105402 (S-Methoprene)
		067501 (Piperonyl Butoxide)

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

Byron T. Backus
2-5-2009
M Hasha

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

Registrant: WELLMARK INTERNATIONAL

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
128965 Etofenprox	30.0
105402 S-Methoprene	3.6
067501 Piperonyl Butoxide	5.0
Other Ingredient(s):	61.4
TOTAL	100.0

ACTION REQUESTED: The Risk Manager requests:

"Attached please find two volume COMPANION ANIMAL SAFETY STUDY with DOGS."

BACKGROUND:

This package consists of a two-volume companion animal safety study in adult dogs (MRID 47518510). In addition, there is a report amendment (MRID 47578401, sent in under DP Barcode 359984) with a corrected page.

COMMENTS AND RECOMMENDATIONS:

The study in MRID 47518510 is classified as acceptable. While there are a number of minor deficiencies in the reporting of this study, it does demonstrate that there is at least a 5X margin of safety associated with the maximum proposed use application rate (0.66 mL/kg). This study does satisfy the 870.7200 guideline requirements for a companion animal safety study in adult dogs, and it does support the use of the proposed product RF2042 [CDSO] on adult dogs with the following label [use] modifications: The statement: "Do not reapply product for 30 days unless re-treatment is required." should be modified to something "Do not reapply product for 30 days unless re-treatment is required, but not sooner than 8 days after the previous treatment." It is also noted that the label claims: "Can be used in households with dogs and cats" and "Based on testing, accidental exposure to cats will not cause serious harmful effects" [presumably based on additional studies which have been submitted to the Agency] have not yet been evaluated and accepted. The remainder of the label should be consistent with Pesticide Registration (PR) Notice 96-6. For additional comments, refer to the executive summary of the attached DER.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 5, 2009
Risk Manager (EPA): 13

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety – Adult Dog; OPPTS 870.7200

TEST MATERIAL(S): JM982 Spot On, Lot No. TM502-7-1; containing 9.98-10.04% S-Methoprene, 54.68-54.98% Piperonyl Butoxide, 29.83-30.14% Etofenprox [Nominal concentrations: 10.0% S-Methoprene; 60.0% Piperonyl Butoxide; and 30.0% Etofenprox]. From information received from the registrant February 4, 2009 the test material had a density of 1.0482 g/mL at 20°C. The RF2042 solvent system had a density of 0.9487, while the corn oil had a density of 0.9179 g/mL.

PRODUCT: RF2042, with a label declaration of 3.6% S-Methoprene; 5.0% Piperonyl Butoxide; and 30.0% Etofenprox. Note: the material tested had higher concentrations of two of the active ingredients relative to the proposed product; according to the 870.7200 Guidelines: "Because of the practice of combining several pesticides in one product, a procedure has been proposed whereby maximum concentrations of multiple active ingredients have been used to determine the margin of safety of end-use products. This practice has been referred to as the max/tox procedure."

CITATION: Slone, R. (2008) Safety of an Experimental JM982 Spot-on Administered Topically to Adult Dogs. Project Number: PLRS/0750, 3323. August 8, 2008. Unpublished study prepared by Professional Laboratory and Research Services, Inc., Corapeake, NC 27926. 661 p. MRID 47518510

SPONSOR: Wellmark International, West Schaumburg, IL 60173

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 47518510), 5 groups, each containing 12 (6/sex) young adult beagles (196-268 days old at the time of first treatment; Day -1 weights: males: 7.7-11.4 kg; females: 6.3-9.9 kg; hair length: 1.0-3.0 cm; source: Ridglan Farms, Inc.) were dermally exposed to either JM982 or one of two control substances (the product solvent or corn oil). Group A (1X) dogs received single 0.66 mL/kg dosages of JM982 Spot On on days 0 and 8; Group B (3X) dogs received three (~1 hour apart) 0.66 mL/kg dosages of JM982 on days 0 and 8; Group C (5X) dogs were treated with five (~1 hour apart) 0.66 mL/kg dosages of JM982 on days 0 and 8, Group D dogs received five (~1 hour apart) dosages of the product solvent control (RF2042), while Group E dogs received 5 (~1 hour apart) dosages of corn oil. Because of the large number of dogs, the study was conducted in two replicates, each consisting of 3 males and 3 females/group. The study was terminated on Day 23 (15 days after the second treatment).

According to proposed label directions the proposed product, RF2042 (3.6% S-Methoprene; 5.0% Piperonyl Butoxide; and 30.0% Etofenprox; note that the percentages of S-Methoprene and Piperonyl Butoxide are considerably lower than the tested formulation) would be applied at the rate of 1.5 cc for small dogs (5-15 lbs), 3.0 cc for medium dogs (15-30 lbs), 6.0 cc for large dogs (30-80 lbs), and 8.0 cc for extra large dogs (80-150 lbs). Label directions specify to apply the product evenly at two spots (small dogs), three spots (medium dogs), and to four or five spots

(large and extra large dogs) on the top of the back from the shoulder to the base of the tail, parting the hair to apply directly to the skin. In this study the test material was applied (in approximately equal amounts) to three spots on each animal (between the shoulder blades, to the back at the middle of the ridgeline and near the base of the tail). No runoff was observed in any dog.

An application rate of 1.5 cc for a 5 lb dog = 0.66 mL/kg, and this is the maximum proposed rate (3.0 cc for a 15 lb dog = 0.44 mL/kg; 6.0 cc for a 30 lb dog = 0.44 mL/kg; and 8.0 cc for an 80 lb dog = 0.22 mL/kg.

The proposed label includes the statement: "Do not reapply product for 30 days unless retreatment is required."

The dogs are reported (p. 15 of MRID 47518510) to have been observed at least twice daily during the study, and at 1-hour intervals for four hours following the last application on Day 0. However, the individual daily observations (pages 36-40 of MRID 47518510) indicate only one observation/day/dog from Day 1 through 22.

Blood samples were taken on Days -1, 1 and 9. The report does not state whether or not the dogs were fasted prior to collections. From information received 01/27/2009 by this reviewer the dogs were not specifically fasted, bu the blood samples were taken before they were given their ration of food for the day.

The most common observation (seen in all dogs of all 5 groups following the second treatment) was oily fur; this was gone by day 13 in Group A. Two Group C females were observed scratching on day 3, as was one group D female on days 0 and 8. Other findings (considered sporadic) were ocular discharge (one Group A male on days 2-3), watery and/or loose stools (one Group A male on day 14, one Group E male on days 4-5), bloody mucous in stools (one Group B male on day 14), and vomit (one Group E male on day 3

Dogs were individually weighed on Days -8, -1, 7, 9, 15 and 22.

There was no indication from the weight data of any dose-related adverse effects. One female (DUK7) in Group QA (1X) is reported to have lost weight (from 7.2 kg on day 7 to 6.1 kg on day 9), but this dog weighed 7.1 kg on day 15. This animal did lose weight (from 7.4 kg on day -1 to 6.9 kg on day 22) during this study, as did Group B male ZLP7 (9.0 kg on day -1, 8.8 kg on day 22), and Group B female SSK7 (8.1 kg on day -1, 7.8 kg on day 22). All the others (including all Group C dogs) either gained or maintained weight during this period.

Based on body weight, dogs were given 175 to 304 g of food/day. Generally, dogs ate their entire ration, and what is reported are the 21 occasions when individual dogs did not completely consume the food that was offered. Ten of these occasions involved a single female (KIQ7) in Group A, six involved a single female (LSQ7) in Group B, two involved a male (PYP7) in Group C, two involved a male (KXR7) in Group E, and one involved a male (VUP7) in Group B. There was no indication of an association between when treatment occurred and incomplete food consumption (the earliest incomplete food consumption was on Day 4, involving the Group E male; the Group A female showed incomplete food consumption on Days 8, 9 and 10, but this female also showed incomplete food consumption on Days 7, 15-17, 19, 20 and 22). The two females with the most occurrences of incomplete food consumption showed slight body weight gains in the period from Day 9 to 15 (8.2 to 8.6 kg and 9.3 to 9.5 kg). The only possible

indication of a dose-related effect involved Group C male PYP7 which did not consume the full ration on Days 9 and 10 (the two days following the second application of JM982 at 5X).

Although there were a number of statistically significant changes between pretreatment and post-treatment hematology and clinical chemistry parameters, most individual values remained well within the reference ranges, there was no dose-relationship, and the changes were not biologically significant. The exceptions involving Group C were APTT (3 dogs in this group showed an APTT on day 9 that was below the reference range), chloride (8 dogs in this group showing values outside the reference range on day 1, and GGT (7 dogs in this group showing values outside the reference range on day 9). The three day 9 APTT values (14.0, 15.0 and 14.9 seconds) were slightly lower than the reference range (15.2 to 24.3 seconds). The eight day 1 chloride values (ranging from 119-124) were slightly elevated with respect to the reference range (109-118), while the seven day 9 GGT values (ranging from 8-12) were also elevated with respect to the reference range (0-7). For APTT, clotting disorders generally result in a longer APTT, rather than a shorter one. Specimens obtained via traumatic venipuncture (or involving slower blood collection) may introduce tissue component contamination which may shorten the APTT. For the day 1 chloride values, four dogs in Group D (solvent control) and three in Group E (corn oil) also showed slightly elevated chloride levels (ranging from 119-121). However, all of the Group C dogs were within the reference range for chloride on day 9 (one day after the second treatment), as were all in the study except for two dogs (one in group D and one in E). For GGT, a number of dogs showed elevated levels of activity on day 9 (Group A: 3; Group B: 5, Group C: 7, Group D: 4; Group E: 3). The values in Group C dogs ranged from 8-12 (reference range: 0-7). GGT testing is usually performed to differentiate between liver or bone disease when ALP levels are elevated (hepatobiliary disease is generally the primary reason for increased GGT activity); however, there is no indication here of concurrent increased ALP activity, and the GGT findings must be considered as sporadic and/or not significant. Since the unusually high ALT value of 429 U/L reported in one Group C male was only observed on Day 1, and had fallen to 67 U/L on Day 9 (following the second application), it can be considered to be sporadic and not related to exposure to the test material.

It is concluded that while there was a cosmetic effect ("oily fur") associated with application of the test material even at the 1X (use) rate, there were no conclusive indications of any systemic toxicity, other than possibly that with Group C male PYP7 which did not consume the full ration on Days 9 and 10 (the two days following the second application of JM982 at 5X). There may be a localized sensation, as two Group C females were observed scratching on day 3, as was one group D female on days 0 and 8) and a 5X margin of safety has been established for this formulation in adult dogs.

This study is classified as acceptable. While there are a number of minor deficiencies in the reporting of this study, it does demonstrate that there is at least a 5X margin of safety associated with the maximum proposed use application rate (0.66 mL/kg). This study does satisfy the 870.7200 guideline requirements for a companion animal safety study in adult dogs, and it does support the use of the proposed product RF2042 [CDSO] on adult dogs with the following label [use] modifications: The statement: "Do not reapply product for 30 days unless re-treatment is required." should be modified to something "Do not reapply product for 30 days unless re-treatment is required, but not sooner than 8 days after the previous treatment." It is also noted that the label claims: "Can be used in households with dogs and cats" and "Based on testing, accidental exposure to cats will not cause serious harmful effects" [presumably based on additional studies which have been submitted to the Agency] have not yet been evaluated and

accepted. The remainder of the label should be consistent with Pesticide Registration (PR) Notice 96-6.

COMPLIANCE: Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality Claims (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

A. MATERIALS

1. Test material: JM982 Spot On, Lot No. TM502-7-1; containing 9.98-10.04% S-Methoprene, 54.68-54.98% Piperonyl Butoxide, 29.83-30.14% Etofenprox [Nominal concentrations: 10.0% S-Methoprene, 60.0% Piperonyl Butoxide, and 30.0% Etofenprox]. Density = 1.0482 g/mL (at 20°C.).

   Description: A Liquid.
   Lot No.: Lot No. TM502-7-1; expiry date: 18 October 2008
   Storage: Packaged in an amber bottle; stored at room temperature

   Solvent control: RF2042
   Lot No.: TM500: 196-1; expiry date: 4 October 2008; density = 0.9487 g/mL (at 20°C.).
   Storage: Packaged in an amber bottle; stored at room temperature

   Corn oil: Corn oil solvent
   Lot No.: TM500: 198-1; expiry date: 3 October 2008; density = 0.9179 g/mL at 20°C.
   Storage: Packaged in an amber bottle; stored at room temperature

2. Administration: Topical (Spot-On) on Days 0 and 8.

3. Test animals
   Species: Dog
   Breed: Beagle
   Ages and weights at study initiation (Day 0, first day of dosing): males: 196-236 days; females: 216-272 days; day -1 body weights: males: 7.7-11.4 kg; females:
   Source: Ridglan Farms, Inc.
   Housing: Individually in stainless steel cages or concrete-floored runs during the study; these cages and runs were cleaned daily.
   Diet: Purina adult dog food
   Water: "Fresh water,...free of contaminants, was provided..."

4. Environmental conditions
   Temperature: Not reported
   Humidity: Not reported
   Air changes: Not reported
   Photoperiod: Not reported
   Acclimation period: 14 days

II. STUDY DESIGN

A. IN LIFE DATES

From p. 8: Start of Dosing: February 12, 2009; Last Data Collection: April 24, 2008

B. ANIMAL ASSIGNMENT / DOSAGE AND ADMINISTRATION

The dogs were acclimated for 14 days. They were vaccinated and dewormed prior to shipment. No vaccinations were administered after arrival of the test laboratory.

From p. 14: "The dogs were separated by gender and ranked from high to low based on the body weights. Ties were broken by ranking alphabetically by animal ID. Five slips of paper each identified with one of five letters representing the five treatment groups (A, B, C, D, or E) were placed into a container and randomly drawn one at a time. The first letter drawn was assigned to the first male listed, the second letter drawn was assigned to the second male listed and so forth until all the letters had been drawn from the container. The slips were returned to the container and the procedure repeated until 15 of the male dogs in each replicate had been assigned to a treatment group. The female dogs were randomized in the same manner."

From p. 14: "The [1X] application rate for the test, product solvent control substance and corn oil control was 0.66 mL/kg body weight… Using either a 12 cc, 6 cc and/or 1 cc syringe, based on the dosage volume, each dog was treated with a dose volume appropriate to its weight and test substance/control. The ID of each dog was confirmed prior to treatment. The syringe contents (dose) were applied to three spots in equally approximate amounts between the shoulder blades, to the back at the middle of the ridgeline and near the base of the tail. The tip of the syringe was used to part the hair and the substance was applied directly to the skin… No runoff was noted on any of the dogs in any treatment group."

TABLE 1. Study design

Group and Sex	Number of Animals	Mean Weight (kg) on Day -1	Mean Amount (mL) and Substance Applied Day 0	Mean Weight (kg) on Day 7	Mean Amount (mL) and Substance Applied Day 8
A					
Males	6	9.38	6.18 (1X JM982)	9.30	6.17 (1X JM982)
Females	6	8.52	5.62 (1X JM982)	8.45	5.57 (1X JM982)
B					
Males	6	9.45	18.65 (3X JM982)	9.40	18.60 (3X JM982)
Females	6	8.05	15.95 (3X JM982)	7.88	15.50 (3X JM982)
C					
Males	6	9.35	30.83 (5X JM982)	9.25	30.50 (5X JM982)
Females	6	8.52	28.08 (5X JM982)	8.45	27.83 (5X JM982)
D					
Males	6	9.17	30.25 (5X solvent)	9.27	30.58 (5X solvent)
Females	6	8.13	26.75 (5X solvent)	8.03	26.42 (5X solvent)
E					
Males	6	9.42	31.00 (5X corn oil)	9.40	30.92 (5X corn oil)
Females	6	8.40	27.67 (5X corn oil)	8.20	27.00 (5X corn oil)

C. DOSE SELECTION RATIONALE

Not stated, however, the dosages (1X, 3X and 5X of the proposed spot-on) are consistent with the 870.7200 Guidelines , as is the use of a concurrent vehicle (solvent) control group and a negative control (corn oil). As noted on p. 9 of MRID 47518510: "The additional 0X control (corn oil) was added at the request of the EPA." The dosage rate of 0.66 mL/kg is consistent with the maximum dosage rate on the proposed label (1.5 mL for a 5 lb dog [= 1.5 mL for a 2.268 kg dog = 0.66 mL/kg].

There is some inconsistency in the proposed labeling, as according to the NET CONTENTS the package will contain either one 1.5 cc or one 3.0 cc or one 6 cc or one 8.0 cc applicator tube, but on the second page there is a note that "Each package contains sufficient tubes/applicators for [X] applications." In addition, it is indicated that this is a multi-application pack. Application directions include a specification to apply the entire content of the applicator to four or five spots on the top of the dog's back from the shoulder to the base of the dog's tail, "and gently squeeze to expel a portion of the solution on the skin [perhaps it would be better to state to apply all the solution to the skin at four or five spots on the top of the dog's back…]."

D. EXPERIMENTAL DESIGN

From p. 12 of MRID 47518510: "Each dog was observed daily for the 14 days preceding Test Day 0…" From p. 15: "The dogs were observed at ~1, 2, 3 and 4 hours post-treatment, beginning after the last treatment and twice daily thereafter for the duration of the observation period. Recorded observations included any signs of adverse reactions to treatment, including dermal irritation."

Individual dogs were weighed on Days -8, -1 (the day before first dosing), 7 (the day before second dosing), 15 and 22.

Individual food consumption was measured daily beginning on Day -7 and through Day 22. From p. 12: "Based on body weight, the animals were given from 175 to 304 g of food per day during the study." From p. 21: "Only those instances when the total amount of food offered was not consumed were tabulated…"

E. HEMATOLOGY AND CLINICAL CHEMISTRY

Blood samples were collected from each dog once pretest (Day -1), and postdose on Days 1 and 9. From information received 01/27/2009 by this reviewer the dogs were not specifically fasted, but the blood samples were taken before they were given their ration of

food for the day. The CHECKED (X) parameters were examined:

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Absolute reticulocytes
	Blood clotting measurements		Percent reticulocytes
	(Thromboplastin time)	X	Heinz bodies
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin (Alb)*
X	Chloride*	X	Blood creatinine (Crea)*
	Magnesium	X	Blood urea nitrogen (BUN)*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total bilirubin (T Bil)*
	ENZYMES	X	Direct bilirubin (D Bil)*
X	Alkaline phosphatase(ALPor ALK)*	X	Total serum protein (TP)*
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		Albumin/Globulin (A/G) ratio
X	Serum alanine aminotransferase (ALT or SGPT)*		Lipase
X	Serum aspartate aminotransferase(AST or SGOT)*		
X	Gamma glutamyl transferase(GGT)		
X	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

From p. 50 of MRID 47518510: "All analyses and calculations were performed using SAS Version 8.2. Statistical significance was declared at a two-side p-value of 0.05."

"Since this is a safety study, the emphasis of the statistical analysis was on the change from baseline parameters in each of the hematology and clinical chemistry parameters..." Body weight was similarly evaluated.

G. DISPOSITION OF ANIMALS

From p. 18 of MRID 47518510: "At the conclusion of the study, all dogs were returned to the PLRS colony." According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

H. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

Refer to Table 1 of this DER. Dogs in Group A received 1X the test formulation at a rate of 0.66 mL/kg; dogs in Group B received 3X the test formulation at a total (cumulative) rate of 1.98 mL/kg; those in Group C received 5X the test formulation at a total (cumulative) rate of 3.30 mL/kg. Dogs in Group D received a cumulative total of 3.30 mL/kg of the formulation solvents, while dogs in Group E received a cumulative total of 3.30 mL/kg corn oil.

B. MORTALITY

There was no mortality, with all dogs surviving the 22-day observation period.

C. CLINICAL SIGNS

It is stated (p. 22 of MRID 475185610) that: "The most common observation was oily fur. The test materials were oily substances and since the dogs were treated twice, once on Test Day 0 and again on Test Day 8, the fur at the application site was oily following each application. Oily fur is considered to be a cosmetic effect that is the direct result of topically applying an oily test substance and is not considered to be an abnormal condition or reaction..."

"All clinical signs that were noted occurred in single animals and lasted no longer than two days. One male in Group A had an ocular discharge on Test Days 2 and 3 and one male dog [also in Group A] had loose stools on Test Day 14. One male dog in Test Group B had bloody mucous in the stool on Test Day 14. Two female dogs in Test Group C were excessively scratching their sides on Test Day 0 [note: according to information on p. 38 this scratching occurred in these two females on Day 3] and one female dog in Test Group D was observed scratching its back on Test Days 0 and 8, both at one hour post-treatment [this is consistent with information presented on p. 39]. One male in Group E had watery/loose stools on Test Days 4/5 respectively, one male dog in Test Group E vomited on Test Day 3, and one female dog in Test Group E had a swelling between the

toes on Test Day 22. None of these clinical signs, other than perhaps scratching, were treatment-related."

D. BODY WEIGHT AND WEIGHT GAIN

From p. 21 of MRID 47518510: "The mean body weight changes from Test Day -1 to each of Test Days 7, 9, 15 and 22 were similar across the five treatment groups." Refer to Table 2, below, for group mean body weights. Group A female DUK7 is reported (see p. 32) to have dropped from 7.2 kg on Day 7 to 6.1 kg on Day 9, but then weighed 7.1 kg on Day 15.

Table 2. Group Mean Body Weights (kg) ± S.D.

Group and Dosage Level	Day -1	Day 7	Day 9	Day 15	Day 22
Group A (1X) Males	9.38 ± 1.28	9.30 ± 1.25	9.23 ± 1.36	9.42 ± 1.41	9.73 ± 1.53
Group A (1X) Females	8.52 ± 1.03	8.45 ± 1.02	8.27 ± 1.34	8.77 ± 1.17	8.82 ± 1.26
Group A (1X) Combined	8.95 ± 1.19	8.88 ± 1.18	8.75 ± 1.38	9.09 ± 1.28	9.28 ± 1.42
Group B (3X) Males	9.45 ± 1.00	9.40 ± 1.17	9.43 ± 1.25	9.62 ± 1.19	10.08 ± 1.42
Group B (3X) Females	8.05 ± 0.85	7.88 ± 0.91	7.88 ± 0.98	8.07 ± 1.01	8.23 ± 1.04
Group B (3X) Combined	8.75 ± 1.15	8.64 ± 1.27	8.66 ± 1.35	8.84 ± 1.33	9.16 ± 1.53
Group C (5X) Males	9.35 ± 0.93	9.25 ± 1.04	9.40 ± 0.95	9.70 ± 1.22	9.95 ± 1.10
Group C (5X) Females	8.52 ± 1.06	8.45 ± 1.08	8.55 ± 1.20	8.77 ± 1.20	8.97 ± 1.20
Group C (5X) Combined	8.93 ± 1.05	8.85 ± 1.10	8.98 ± 1.12	9.23 ± 1.26	9.46 ± 1.21
Group D (5X solvent control) Males	9.17 ± 1.11	9.27 ± 1.12	9.30 ± 1.22	9.43 ± 1.32	9.72 ± 1.23
Group D (5X solvent control) Females	8.13 ± 0.94	8.03 ± 0.95	8.13 ± 1.10	8.38 ± 1.10	8.65 ± 1.06
Group D (5X solvent control) Combined	8.65 ± 1.12	8.65 ± 1.18	8.72 ± 1.26	8.91 ± 1.26	9.18 ± 1.23
Group E (5X corn oil) Males	9.42 ± 0.95	9.40 ± 0.87	9.35 ± 0.85	9.57 ± 0.88	9.75 ± 0.82
Group E (5X corn oil) Females	8.40 ± 0.91	8.20 ± 1.13	8.27 ± 1.07	8.45 ± 1.12	8.67 ± 1.15
Group E (5X corn oil) Combined	8.91 ± 1.03	8.80 ± 1.15	8.81 ± 1.08	9.01 ± 1.12	9.21 ± 1.11

Group mean body weights and standard deviations calculated from data presented on pages 32-34 of MRID 47518510.

F. FOOD CONSUMPTION

From p. 21 of MRID 47518510: "The treatment regimens did not affect the food consumption of the study dogs. Only those instances when the total amount of food offered was not consumed were tabulated... Over the course of the study four dogs (two males and two females) did not consume all of the food offered. One male (VUP7) in Group B (3X) did not eat all of food on one occasion [this was on Day 11, when this dog consumed 227.1 g of the 270 g offered] and one male dog (PYP7) in Group C (5X) did not eat the full ration on two consecutive days [this was on Days 9 and 10, when this dog ate 194.5 and 141.7 g, respectively, with 304 g offered on each day]. Two females (KIQ7 and LSQ7) consistently did not consume all of the food presented. KIQ7 in Group A (1X) consumed less from Test Day 7 to the end of the study [Test Days 7, 8, 9, 10, 15, 16, 17, 19, 20 and 22] and LSQ7 in Group B (3X) consumed less than offered from Day 14 [Days 14, 17, 18, 20, 21 and 22] to the termination of the study." It is noted that, according to information on p. 35, male KXR7 in Group E did not consume the full amount of food offered on Days 4 and 5.

The only possible indication of a dose-related effect involved Group C male PYP7 which did not consume the full ration on Days 9 and 10 (the two days following the second application of JM982 at 5X).

G. HEMATOLOGY AND CLINICAL CHEMISTRY PARAMETERS

Although a number of statistically significant changes were observed in certain hematology (including RBC, hemoglobin, hematocrit, MCV, and MCHC) and clinical chemistry (including AST, GGT, amylase, total bilirubin and albumin) values on days 1 and/or 9 relative to pre-exposure values, most animals remained within the reference range or there were no indications of a dose-response (effects were similar in the JM982, solvent and corn oil groups). The exceptions (involving elevated numbers of animals in Group C outside the reference range) included MCHC on day 9, APTT on day 9, sodium on day 1, potassium on day 1, chloride on day 1, and GGT on day 9.

Table 3. Number of Hematology/Clinical Chemistry Values Outside Reference Range*

Parameter	Day	Group A	Group B	Group C	Group D	Group E
MCHC	-1	0	0	0	0	0
	+1	0	0	1	2	1
	+9	2	6	10	7	7
APTT	-1	0	0	0	0	0
	+1	0	0	0	0	1
	+9	0	1	3	0	1
Sodium	-1	0	0	0	0	0
	+1	2	3	6	4	6
	+9	1	1	1	0	0
Potassium	-1	0	0	0	0	0
	+1	1	1	3	0	0
	+9	0	1	0	0	0
Chloride	-1	0	0	0	0	0
	+1	1	3	8	4	3
	+9	0	0	0	1	1
GGT	-1	0	0	0	0	0
	+1	0	0	0	0	0
	+9	3	5	7	4	3

*Taken from the tables on p. 57 and 58 of MRID 47518510; it is noted that the reference ranges in these tables differ from those on the data sheets from Anilytics Inc. (the reference range for MCHC is given as 33.2-35.5[%] on p. 57, and from 31-36[%] on p. 127; the reference range for APTT is given as 15.2-24.3 [seconds] on p. 57, but as 10.3-15 [seconds] on p. 250, which seems to be too low for dogs [dogs generally have APTT values somewhat lower than humans, but 15.2-24.3 seconds for this species seems to be a more valid range than 10.3-15 seconds]; the reference range for sodium is given as 145-150 [meq/L] on p. 58, but as 141-152 [meq/L] on p. 142 etc.).

As shown in Table 3 above, increased out-of-range incidences (including for MCHC and GGT on day 9) in Group C were associated with increased out-of-range incidences for the same parameters in Groups D and E (the 5X solvent and 5X corn oil groups, respectively). Therefore, these findings are considered to be unrelated to exposure to the JM982.

From p. 25 of MRID 47518510: "Mean amylase activity was lower than the…oil control group in the 1X and 5X treatment groups on Test Day 1. No significant differences between the baseline values of control groups were observed at 3X on Test Day 1. Test Day 9 amylase activity was lower in groups 1X and 3X but not in the 5X group. The lower mean amylase activity did not occur in a dose-related manner and was not considered related to the treatment."

From p. 26 of MRID 47518510: "It is noted that there was an unusually high value of 429 [U/L] reported for ALT in Dog PYP7 (Test Group C) on Test Day 1. This value was confirmed by the clinical laboratory with an explanation that this data was not flagged as an outlier due to the fact that it was within the linearity of the equipment being used. The respective values on Test Days -1 and 9 were 48 and 67 [see pages 148 and 220]." As this anomalous value was observed only on Day 1, and not Day 9 (following the second application), it can be considered to be sporadic and not related to exposure to the test material.

H. NECROPSY FINDINGS

As there were no mortalities, no necropsies were performed.

IV. DISCUSSION

In a companion animal safety study (MRID 47518510), 5 groups, each containing 12 (6/sex) young adult beagles (196-268 days old at the time of first treatment; Day -1 weights: males: 7.7-11.4 kg; females: 6.3-9.9 kg; hair length: 1.0-3.0 cm; source: Ridglan Farms, Inc.) were dermally exposed to either JM982 or one of two control substances (the product solvent or corn oil). Group A (1X) dogs received single 0.66 mL/kg dosages of JM982 Spot On on days 0 and 8; Group B (3X) dogs received three (~1 hour apart) 0.66 mL/kg dosages of JM982 on days 0 and 8; Group C (5X) dogs were treated with five (~1 hour apart) 0.66 mL/kg dosages of JM982 on days 0 and 8, Group D dogs received five (~1 hour apart) dosages of the product solvent control (RF2042), while Group E dogs received 5 (~1 hour apart) dosages of corn oil. Because of the large number of dogs, the study was conducted in two replicates, each consisting of 3 males and 3 females/group. The study was terminated on Day 23 (15 days after the second treatment).

According to proposed label directions the product, RF2042 (3.6% S-Methoprene; 5.0% Piperonyl Butoxide; and 30.0% Etofenprox) would be applied at the rate of 1.5 cc for small dogs (5-15 lbs), 3.0 cc for medium dogs (15-30 lbs), 6.0 cc for large dogs (30-80 lbs), and 8.0 cc for extra large dogs (80-150 lbs). Label directions specify to apply the product evenly at two spots (small dogs), three spots (medium dogs), and to four or five spots (large and extra large dogs) on the top of the back from the shoulder to the base of the tail, parting the hair to apply directly to the skin. In this study the test material was applied (in approximately equal amounts) to three spots on each animal (between the shoulder blades, to the back at the middle of the ridgeline and near the base of the tail). No runoff was observed in any dog.

An application rate of 1.5 cc for a 5 lb dog = 0.66 mL/kg, and this is the maximum proposed rate (3.0 cc for a 15 lb dog = 0.44 mL/kg; 6.0 cc for a 30 lb dog = 0.44 mL/kg; and 8.0 cc for an 80 lb dog = 0.22 mL/kg.

The proposed label includes the statement: "Do not reapply product for 30 days unless retreatment is required."

The dogs are reported (p. 15 of MRID 47518510) to have been observed at least twice daily during the study, and at 1-hour intervals for four hours following the last application on Day 0. However, the individual daily observations (pages 36-40 of MRID 47518510) indicate only one observation/day/dog from Day 1 through 22.

Blood samples were taken on Days -1, 1 and 9. The report does not state whether or not the dogs were fasted prior to collections; the company contact, From information received 01/27/2009 by this reviewer the dogs were not specifically fasted, but the blood samples were taken before they were given their ration of food for the day.

The most common observation (seen in all dogs of all 5 groups following the second treatment) was oily fur; this was gone by day 13 in Group A. Two Group C females were

observed scratching on day 3, as was one group D female on days 0 and 8. Other findings (considered sporadic) were ocular discharge (one Group A male on days 2-3), watery and/or loose stools (one Group A male on day 14, one Group E male on days 4-5), bloody mucous in stools (one Group B male on day 14), and vomit (one Group E male on day 3

Dogs were individually weighed on Days -8, -1, 7, 9, 15 and 22.

There was no indication from the weight data of any dose-related adverse effects. One female (DUK7) in Group QA (1X) is reported to have lost weight (from 7.2 kg on day 7 to 6.1 kg on day 9), but this dog weighed 7.1 kg on day 15. This animal did lose weight (from 7.4 kg on day -1 to 6.9 kg on day 22) during this study, as did Group B male ZLP7 (9.0 kg on day -1, 8.8 kg on day 22), and Group B female SSK7 (8.1 kg on day -1, 7.8 kg on day 22). All the others (including all Group C dogs) either gained or maintained weight during this period.

Based on body weight, dogs were given 175 to 304 g of food/day. Generally, dogs ate their entire ration, and what is reported are the 21 occasions when individual dogs did not completely consume the food that was offered. Ten of these occasions involved a single female (KIQ7) in Group A, six involved a single female (LSQ7) in Group B, two involved a male (PYP7) in Group C, two involved a male (KXR7) in Group E, and one involved a male (VUP7) in Group B. There was no indication of an association between when treatment occurred and incomplete food consumption (the earliest incomplete food consumption was on Day 4, involving the Group E male; the Group A female showed incomplete food consumption on Days 8, 9 and 10, but this female also showed incomplete food consumption on Days 7, 15-17, 19, 20 and 22). The two females with the most occurrences of incomplete food consumption showed slight body weight gains in the period from Day 9 to 15 (8.2 to 8.6 kg and 9.3 to 9.5 kg). The only possible indication of a dose-related effect involved Group C male PYP7 which did not consume the full ration on Days 9 and 10 (the two days following the second application of JM982 at 5X).

Although there were a number of statistically significant changes between pretreatment and post-treatment hematology and clinical chemistry parameters, most individual values remained well within the reference ranges, there was no dose-relationship, and the changes were not biologically significant. The exceptions involving Group C were APTT (3 dogs in this group showed an APTT on day 9 that was below the reference range), chloride (8 dogs in this group showing values outside the reference range on day 1, and GGT (7 dogs in this group showing values outside the reference range on day 9). The three day 9 APTT values (14.0, 15.0 and 14.9 seconds) were slightly lower than the reference range (15.2 to 24.3 seconds). The eight day 1 chloride values (ranging from 119-124) were slightly elevated with respect to the reference range (109-118), while the seven day 9 GGT values (ranging from 8-12) were also elevated with respect to the reference range (0-7). For APTT, clotting disorders generally result in a longer APTT, rather than a shorter one. Specimens obtained via traumatic venipuncture (or involving slower blood collection) may introduce tissue component contamination which may shorten the APTT. For the day 1 chloride values, four dogs in Group D (solvent control) and three in Group E (corn oil) also showed slightly elevated chloride levels (ranging from 119-121). However, all of the Group C dogs were within the reference range for chloride on day 9 (one day after the second treatment), as were all in the study except for two dogs (one in group D and one in

E). For GGT, a number of dogs showed elevated levels of activity on day 9 (Group A: 3; Group B: 5, Group C: 7, Group D: 4; Group E: 3). The values in Group C dogs ranged from 8-12 (reference range: 0-7). GGT testing is usually performed to differentiate between liver or bone disease when ALP levels are elevated (hepatobiliary disease is generally the primary reason for increased GGT activity); however, there is no indication here of concurrent increased ALP activity, and the GGT findings must be considered as sporadic and/or not significant. Since the unusually high ALT value of 429 U/L reported in one Group C male was only observed on Day 1, and had fallen to 67 U/L on Day 9 (following the second application), it can be considered to be sporadic and not related to exposure to the test material.

It is concluded that while there was a cosmetic effect ("oily fur") associated with application of the test material even at the 1X (use) rate, there were no conclusive indications of any systemic toxicity, other than possibly that with Group C male PYP7 which did not consume the full ration on Days 9 and 10 (the two days following the second application of JM982 at 5X). There may be a localized sensation, as two Group C females were observed scratching on day 3, as was one group D female on days 0 and 8) and a 5X margin of safety has been established for this formulation in adult dogs.

This study is classified as acceptable. While there are a number of minor deficiencies in the reporting of this study, it does demonstrate that there is at least a 5X margin of safety associated with the maximum proposed use application rate (0.66 mL/kg). This study does satisfy the 870.7200 guideline requirements for a companion animal safety study in adult dogs, and it does support the use of the proposed product RF2042 [CDSO] on adult dogs with the following label [use] modifications: The statement: "Do not reapply product for 30 days unless re-treatment is required." should be modified to something "Do not reapply product for 30 days unless re-treatment is required, but not sooner than 8 days after the previous treatment." It is also noted that the label claims: "Can be used in households with dogs and cats" and "Based on testing, accidental exposure to cats will not cause serious harmful effects" [presumably based on additional studies which have been submitted to the Agency] have not yet been evaluated and accepted. The remainder of the label should be consistent with Pesticide Registration (PR) Notice 96-6.

1. **DP BARCODE:** 359964
2. **PC CODES:** 128965 (Etofenprox); 105402 (S-Methoprene); 067501 (Piperonyl Butoxide)
3. **CURRENT DATE:** February 5, 2009
4. **TEST MATERIAL:** JM982 Spot On, Lot No. TM502-7-1; containing 9.98-10.04% S-Methoprene, 54.68-54.98% Piperonyl Butoxide, 29.83-30.14% Etofenprox [Nominal concentrations: 10.0% S-Methoprene; 60.0% Piperonyl Butoxide; and 30.0% Etofenprox]. From information received from the registrant February 4, 2009 the test material had a density of 1.0482 g/mL at 20°C. The RF2042 solvent system had a density of 0.9487, while the corn oil had a density of 0.9179 g/mL.

Note: this study is being used to support RF2042[CDSO}, with a label declaration of 3.6% S-Methoprene; 5.0% Piperonyl Butoxide; and 30.0% Etofenprox. The material tested had higher concentrations of two active ingredients relative to the proposed product, but this is acceptable as according to the 870.7200 Guidelines: "Because of the practice of combining several pesticides in one product, a procedure has been proposed whereby maximum concentrations of multiple active ingredients have been used to determine the margin of safety of end-use products. This practice has been referred to as the max/tox procedure."

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety/ adult dog / Professional Laboratory and Research Services, Inc., Corapeake, NC / PLRS 0750 / August 8, 2008	47518510 47578401	Five groups, each containing 6M & 6F young adult beagles were dermally exposed to either JM982 Spot-On at 1X (Group A), 3X (Group B), 5X (Group C), 5X solvent control (Group D) or 5X corn oil (Group E) on Days 0 & 8. 1X = 0.66 mL/kg. While there was a cosmetic effect ("oily fur") at even the 1X rate, there were no conclusive signs of toxicity other than possibly that with a Group C male which did not consume a full ration on Days 9 & 10 (the two days following the 2nd application of JM982 at 5X). There may have been a localized sensation, as two Group C females were observed scratching on Day 3 as was one Group D female on Day 0. Study demonstrates there is at least a 5X margin of safety associated with the maximum proposed use application rate (0.66 mL/kg)	-	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

Study Summary Review Outline: Clayton Myers, IB 3-10-09

Decision #: **399095**

DP #: **359985**

MRID: **475784-02**

Title: Evaluate the Speed of Kill of RF-2024B against Ticks and Fleas on Dogs*

*an amended final report to replace MRID 475184-12

Purpose/Objectives:

The study was designed to evaluate the speed of kill of animal pet topical spot on, RF-2042B, against:

American Dog Tick (ADT) adults—residual adulticidal activity
Cat Flea adults—residual adulticidal activity

Materials and Methods:

Animals: 16 healthy dogs, 6 males and 10 females from BerTeck, Inc. colony, of varying ages and weights (1-4 years and 22.2-41.5 lbs). Dogs were not treated with any insecticides within four weeks of Day 0. BerTek standard housing and feeding protocols were used. These 16 dogs were chosen from a group of 20 based on pre-treatment qualification. Dogs exhibiting the best levels of flea retention were chosen.

Test parasites: Cat Fleas were from an in-house colony, ADT from El Laboratories, Soquel, CA.

Test insecticide treatment matches CSF

Design:

2 treatments: a control group (1), and an insecticide treated group (2).

Replicates: 6 dogs in control (group 1) and 10 dogs in insecticide treated (group 2).

Randomization: Dogs were ranked by weight and then listed in that order on a random treatment groups assignment table.

Dosages: 3.0 ml for dogs weighing between 15 and 30 lbs, and 6.0 ml for dogs weighing from 31 to 55 lbs. Material administered to each dog along the dorsal line in

approximately 3 equal spots—one between shoulders, in the middle of the back, and at the base of the tail. There was one application to all dogs in group 2 with no re-treatments.

Infestations: Cat Fleas (100) were applied to each animal 7 days after treatment. ADT (50 each) were applied to each animal 7 days after treatment. All parasites were placed along the dorsal midline from the animal's head to the base of its tail.

Data collection:

Pan counts (from pans placed beneath infested dogs in their cages) of fallen fleas and ticks were conducted approximately 15 min., 30 min., 1 h, 2h, 4h, 8h, 12h, and 24 h after the infestation. Pans were replaced at each count, and fleas and ticks dropping into each pan were scored as live or dead.

Removal counts of fleas and ticks were conducted on day 2 after placement (day 9 after treatment) via finger probing and combing of hair. All fleas and ticks were scored as live or dead.

For all counts, group one was assessed first to avoid cross-contamination of pesticide residues.

Statistics: Only descriptive statistics are given. Geometric means were calculated for each group and then % reduction was calculated by comparing the group 2 mean to the control: % reduction = ([GM ctrl – GM trt]/GM ctrl)*100.

Study Summary of the Results:

"Efficacy of the test substance initiated within minutes of the infesting parasite acquiring a treated host."

After 15 minutes, 38% of infesting fleas and 3.4% of infesting ticks had been eliminated from the treated animals

By 48 hours, all the infesting fleas and >85% of infesting ticks had been eliminated.

Entomologist's Observations and Discussion
While ticks are shown to be 'eliminated' from the animals beginning at the 15 minute count, this does not support a 'within minutes' efficacy claim for ticks.

Flea efficacy is acceptable (100% reduction) within 48 hours of treatment. Tick data are quite variable within group 2, but the overall mean and % reduction are acceptable to support a claim of tick efficacy within 48 hours.

Observations/Discussion:

1. Dog qualifications were done only with fleas and not ticks. OPPTS 810.3300 indicates a tick qualification is preferred. Also, only one species of tick was assessed in this study.

2. There was not a very good range of dog weights, with no dogs <24 lbs and no dogs > 42 lbs. More importantly, all the dogs were listed as hounds with short hair. It would have been preferable to have some longer haired dogs and some large dogs that would have required the higher dosage over a larger volume of hair. Titration of dosages appears to be valid, as it is the same as the connected studies on this product, but it would have been preferable to use dogs that fall into the upper and lower bounds of each of the given weight classifications.

3. While the pan counts for ticks show the numbers of ticks that were dislodged from the host, it doesn't document the live/dead status of ticks (the study indicated there were no live fleas found in the pans). They should provide data on the number that were actually dead via knockdown activity to support their claim of "efficacy within minutes for ticks".

4. Parasite placement was along the dorsal midline of each animal, which also happens to be the same area where treatment was applied 7 days prior. This doesn't meet the standard of 'sufficient anatomical distribution' per OPPTS 810.3300. It might have been better to apply the fleas/ticks to other areas of the body to avoid bias toward the most heavily coated hair, especially given the short time frame over which the study was conducted, and the lack of long-haired dogs in the study. The registrant should explain why they used this approach to treatment.

5. The label states "kills more than 90% of fleas in 8 hours," however this data shows only 54.8% flea reduction at 8 hours. 24 hour reduction is only 58.2%. Reduction over 90% (actually 100%) is seen only at the 48 hour hand removal count. Therefore, the data only support the a claim of 'within 48 hours.'

6. The label claims are acceptable except as noted below:

   Effective on Indoor and Outdoor dogs—Not acceptable, since dogs were not exposed to outdoor conditions in any of the studies.

   [Starts killing fleas and ticks within minutes][Kills more than 90% of fleas in 8 hours]—The first claim is OK if revised to 'within 15 minutes.' The second claim is unacceptable, as 90% of fleas are not killed until 48 hours.

Label Review Summary for 2724-TOA 3/10/09

Effective on Indoor and Outdoor dogs—Not acceptable, since dogs were not exposed to outdoor conditions in any of the studies.

([1][3][4][6] monthly treatments) [1][3][4][5] Months Supply [24][48] doses—Acceptable

Each tube [applicator] kills fleas & ticks for 3 to 4 weeks and kills and repels mosquitoes for 3-4 weeks—Not acceptable. Kills fleas and ticks for up to 3 weeks. Mosquito efficacy varied by species. Claims of 3 to 4 weeks are acceptable killing for *Aedes aegypti*, and *Anopheles quadramaculatus*, but not *Culex quinquefasiatus*. Claims of repellence are acceptable.

Aids in control of ticks for up to 30 days [one month]—Not acceptable. Should be revised to 3 weeks.

Contains an Insect Growth Regulator (IGR) to kill flea eggs and prevent flea development for [more than 10 weeks] up to [75 days][2.5 months]—Acceptable

[Starts killing fleas and ticks within minutes][Kills more than 90% of fleas in 8 hours]—The first claim is OK if revised to 'within 15 minutes.' The second claim is unacceptable, as 90% of fleas are not killed until 48 hours.

Kills 85% of ticks within 48 hours—Acceptable

Dual Action kills adult fleas and prevents flea development—Acceptable

Breaks flea life cycle for [more than 10 weeks] up to [75 days][2.5 months]—Acceptable

Controls reinfestation for [more than 10 weeks] up to [75 days][2.5 months]—Acceptable, if reworded to 'controls flea reinfestation'

[Kills fleas, ticks, mosquitoes, flea eggs, and flea larvae][Dual protection (against fleas and ticks)]—Acceptable

Kills the Deer Tick, which may transmit Lyme Disease—Acceptable

Kills and repels mosquitoes (a major carrier of canine heartworm)—Acceptable if killing is qualified by species, since it doesn't kill *Culex*.

[Kills fleas that may transmit Tapeworm (Dipylidium caninum)]—Acceptable

[With [S-Methoprene] Insect Growth Regulator [IGR} to break flea life cycle]—Acceptable

Convenient, easy to use ACCU-TIP DISPENSER [applicator][tube]—Acceptable

Spreads naturally with dog's movement (skin and hair oils)—Acceptable

Non-Irritating/Coat Conditioning Formula—Non-irritating is acceptable, but a coat conditioning claim might not be allowed: implied use of a pesticide for some some purpose other than killing pests, 40 CFR 156.10.

[Water Resistant][Fast Acting][Long Lasting][Kills Fleas and Ticks by Contact]—Acceptable

[Easy to use] Longer applicator tip for easy application to long-haired dogs—Acceptable

[Can be used in households with dogs and cats]—acceptable

[Based on testing, accidental exposure to cats will not cause serious harmful effects]—Acceptable

[Fresh][Clean][Scent][Smell]—Acceptable

[Reapply monthly][Suitable for year-round use][Month] sticker for home calendar—Acceptable

Sold by [Vets][Veteranarians] for over 30 years—Possibly unacceptable, per PR Notice 93-6: Implied claims of heightened efficacy of a pesticide product by itself or as compared with another product or device are false and misleading.

[Satisfaction Guaranteed or your money back]—Acceptable

RF2042 [CDSO] prevents flea eggs from developing into adult fleas [more than 10 weeks] for up to [75 days][2.5 months]. RF2042 [CDSO] also kills fleas and ticks for 3 to 4 weeks and kills and repels mosquitoes for 3 to 4 weeks—Not acceptable. Kills fleas and ticks for up to 3 weeks. Mosquito efficacy varied by species. Kill claims of 3 to 4 weeks are acceptable for *Aedes aegypti*, and *Anopheles quadramaculatus*, but not *Culex quinquefasiatus*. Repellence claims are acceptable.

RF2042 [CDSO] works by application directly to the dog's/puppy's skin, not to the hair. When applying, manually push aside dog's/puppy's hair to allow direct application to the skin. Do not get this product in dog's eyes or mouth.—Acceptable

Application Instructions are acceptable except item 5 in each list: Do not reapply product for 30 days unless re-treatment is required—There should be a qualifying statement or clarification on what justifies a retreatment.

If necessary, dog may be retreated on week after the initial treatment but do not retreat more than once per month—Again, there should be a clarification on what justifies a retreatment

RF2042 [CDSO] is most effective when used as part of a total flea and tick management program. Use other [Brand Name] products registered for residential area control of these pests in conjunction with this treatment. Monthly treatments are required for optimal control and prevention of fleas.—Acceptable

[The successive feeding activity of fleas on pets may elicit a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with RF2042 [CDSO] rapidly kills fleas and may reduce the incidence of this condition.]—Acceptable

[RF2042 [CDSO] is water resistant and remains efficacious following exposure to rainfall or swimming.]—Unacceptable. Studies demonstrated water resistance in study 11, but did not adequately simulate swimming or the generic claim of 'rainfall.' Water resistance/rainfastness was not demonstrated in study 13 (mosquitoes and deer ticks).

Storage and Disposal statement is adequate if the registrant amends the **if partially filled** statement to "or call 1-800-CLEANUP"

Precautionary Statement is adequate and in compliance with PR Notice 96-6.

Warranty Statement is acceptable.

Label Needs a **First Aid** section

Footnotes

A. This consideration does not apply to PRIA applications that include a request to approve an inert in the fee category. For these PRIA actions, information needs to be submitted to enable the Agency to review the inert approval request and will be a subject of the 21 day content screen. For other types of actions and for fragrances, the answer is only for the Agency's information and current policies, processes, and procedures should be consulted. This worksheet will be updated in the future to be consistent with current policies.

If brand, trade, or proprietary names are being used for some inert ingredients listed on the CSF, alternate names or additional information on the nature of the ingredient(s) should be provided to allow the Agency to determine whether the inert has been approved.

B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.

C. Refer to the list of data requirements. Biopesticide applicants were advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.

Study Summary Review Outline: Clayton Myers, IB 3-10-09

Decision #: 399095

DP #: 357273

MRID: 475185-13

Title: Efficacy of a Combination of Etofenprox and PBO (RF2042B) as a Topical Spot-On (sic) for Dogs Experimentally Infected (sic) with Adult *Ixodes scapularis* Ticks and Three Species of Adult Mosquitoes (*Aedes aegypti, Anopheles quadrimaculatus,* and *Culex quinquefasciatus*).

Purpose/Objectives:

The study was designed to evaluate the efficacy of a topical spot-on RF2042B application on dogs against:

Black-legged tick (BLT) (deer tick)—residual adulticidal activity
Mosquito (*Aedes aegypti*)—residual adulticidal activity and blood feeding
Mosquito (*Anopheles quadrimaculatus*)— residual adulticidal activity and blood feeding
Mosquito (*Culex quinquefasiatus*)— residual adulticidal activity and blood feeding

Materials and Methods:

Animals: 16 healthy dogs, 11 males, 5 females from BerTek, Inc. colony, of varying ages and weights (1-7.5 years, and 12.5-30.2 lbs). Dogs were not treated with any insecticides within four weeks of Day 0. Bertek standard housing and feeding protocol was used.. These 16 dogs were chosen from a group of 20 (12 males, 8 females) based on pre-treatment qualification with flea retention.

Test parasites: Cat fleas from an in-house colony. BLT from Oklahoma State University, Mosquitoes from Benzon Research, Inc.

Test insecticide treatments are not described as fully as in 475185-11

Design:

2 treatments: a control group (1), and an RF2042B insecticide treated group (2)

Replicates: 6 dogs in control (group 1), 10 dogs in insecticide treated (group 2)

Randomization: Dogs were ranked by weight and then assigned to the two groups randomly (per a table in appendix 3, not included in packet—this was discussed under section 9.0 "Deviations.").

Dosages: 1.5 ml for dogs weighing up to 15 lbs, 3.0 mL for dogs weighing from 16 to 30 lbs. Material administered to each dog along the dorsal line in approximately 3 equal spots—one between shoulders, one in the middle of the back, one at the base of the tail. There was one application to all dogs in group 2, with no re-treatments.

Infestations: Ticks were infested *in vitro* onto hair collected on Days 7, 14, 21, 28, 35, 42, and 50 post-treatment. Approximately 1 gram of fur was clipped from approximately the same body site of each study animal and placed in containers with the dog ID and time/date of sampling. Ten ticks (pre-counted in vials) were placed in each container of hair. Containers were stored in a growth chamber. Starved mosquitoes (12 h without sugar solution) were placed in crates within tents. For infestation, approximately 25-50 unfed, unsexed mosquitoes of each species were placed within the tents by aspiration (simultaneously). Once all tents were infested, room lights were turned off until recollection began. Gloves and aspirators were changed between treatments to avoid any cross contamination of insecticide residues.

Data collection:

Ticks: Tick counts were made on days 8, 9 (via visual counts on the same hair) and on days 10 (still same initial hair), 17, 24, 31, 38, 45, and 53 (via a counting tray and disposal of hair and ticks), approximately 24 hours after initial infestation and 72 hours after each weekly re-infestation.

Mosquitoes: Collections were conducted 2 hours after each tent infestation on days 0, 14, 21, 28, 35, and 42 via vacuum aspiration. Mosquitoes were placed in separate labeled vials and scored as alive or dead. For sorting, mosquitoes were sorted by species and sexed, and all females were squashed to determine if feeding occurred.

Statistics: Only descriptive statistics are given. Geometric means were calculated for each group and then % control was calculated by comparing treatment means to the control. % control = ([GM ctrl – GM trt]/GM ctrl)*100

Study Summary of the Results:

Treatment provided >/= 98% in vitro control of BLT through day 45

For *Ae. aegypti*, mortality was >/=95% through day 35 and feeding reduction remained >94% through day 42.

For *Cx. quinquefasiatus*, mortality control was >/= 94% only on day zero, but feeding reduction remained >/= 95% through day 28.

For *An. quadrimaculatus*, mortality was >/= 98% through day 42, and feeding reduction remained >83% through day 35.

Entomologist's Observations/Discussion

Treatment provided >/= 98% in vitro control of BLT through day 45, before falling off to 69% control at day 53.

For *Ae. aegypti*, mortality was >/=95% through day 35 and feeding reduction remained >94% through day 42.

For *Cx. quinquefasiatus*, there was no knockdown efficacy past day zero, but feeding reduction remained >/= 95% through day 28.

For *A. quadriamaculatus*, mortality was >/= 98% through day 42, and feeding reduction remained >83% through day 35.

Observations/Discussion:

1. The qualification of dogs was for flea acceptance, not tick acceptance. Although the tick assay was only *in vitro*, it would have been more appropriate to test acceptance of ticks than to test with fleas, since flea control efficacy was not being evaluated in this study.

2. BLT results are difficult to extrapolate to specific claims because there was no field exposure of dogs, and it's an *in vitro* study."

3. For hair sampling for tick studies, there is no specification of what area the hair was taken from; only that it was 'approximately the same body site' of each dog. There is no indication if sites were changed or randomized. They could have taken hair directly from the site of insecticide treatment and biased the sample.

4. On tick data, the methods indicates that ten ticks were placed on each gram of hair (prepackaged in counted groups of ten) and then mortality was assessed. But if ten were placed, then the data should work out to even percentages (i.e., 10%, 20%, 30%, etc.) for % alive and for mortality for each dog. Either a number different than ten was used , or something was worded wrongly in the methodology, because % alive and mortality numbers are not often even multiples of ten. The registrant needs to explain this discrepancy.

5. "Approximately 25-50" mosquitoes of each species were placed in each cage." There is tremendous variability, and what is the assurance that this was randomized? If, for example, only 25 mosquitoes were placed in the treatment 2 tents, and 50 mosquitoes were placed in the treatment 1 tents, then calculation and comparison of GM's would lead to 50% "mosquito control" even if there was no treatment effect whatsoever. There was also no description given in this study of what the sex ratios are—this is important, because male mosquitoes are not blood feeders and efficacy against males would not be relevant to protection of the dog

from blood feeding. We need to see the raw data on this portion of the study. How many female mosquitoes were evaluated for each species to calculate the % blood feeding and mortality results?

6. OPPTS 810.3300 guidance indicates that there should be 95% knockdown efficacy on mosquitoes to make a mosquito claim. This was not the case for *Culex*, but the data does indicate that blood feeding is reduced there, albeit only through day 28.

7. The label claims "kills and repels" mosquitoes. Based on lack of blood feeding the data show that mosquitoes were "repelled",

8. The label claims are acceptable except as noted below:

   Effective on Indoor and Outdoor dogs—Not acceptable, since dogs were not exposed to outdoor conditions in any of the studies.

   Each tube [applicator] kills fleas & ticks for 3 to 4 weeks and kills and repels mosquitoes for 3-4 weeks—Not acceptable. Kills fleas and ticks for up to 3 weeks. Mosquito efficacy varied by species. Claims of 3 to 4 weeks are acceptable for killing *Aedes aegypti*, and *Anopheles quadramaculatus*, but not *Culex quinquefasiatus*. Claims of repellence are acceptable

   Kills and repels mosquitoes (a major carrier of canine heartworm)—Acceptable if killing is qualified by species, since it doesn't kill *Culex.*

   RF2042 [CDSO] prevents flea eggs from developing into adult fleas [more than 10 weeks] for up to [75 days][2.5 months]. RF2042 [CDSO] also kills fleas and ticks for 3 to 4 weeks and kills and repels mosquitoes for 3 to 4 weeks—Not acceptable. Kills fleas and ticks for up to 3 weeks is acceptable, but mosquito efficacy varied by species. Kill claims of 3 to 4 weeks are acceptable for *Aedes aegypti*, and *Anopheles quadrimaculatus*, but not *Culex quinquefasiatus*. Repellence claims are acceptable.

   [RF2042 [CDSO] is water resistant and remains efficacious following exposure to rainfall or swimming.]—Unacceptable. Water resistance/rainfastness was not demonstrated in this study.

Study Summary Review Outline: Clayton Myers, IB

3/10/09

Decision #: **399095**

DP #: **357273**

MRID: **475185-12**

Title: Evaluate the Speed of Kill of RF-2024B against Ticks and Fleas on Dogs

Refer to the review of MRID 475784-02, which is an amended version of this same report (the only difference in that report was the correction of a typographical error in one of the tables).

Study Summary Review Outline: Clayton Myers, IB 3-10-09

Decision #: **399095**

DP #: **357273**

MRID: **47518511**

Title: Evaluate Ovicidal and Adult Cat Flea Efficacy and Tick Efficacy of RF2042B On Dogs

Purpose/Objectives:

The study was designed to evaluate the efficacy of a topical spot-on RF2042B application on dogs against:

Brown Dog Tick (BDT) adults—residual adulticidal activity
American Dog Tick (ADT) adults—residual adulticidal activity
Cat flea adults—residual adulticidal activity
Cat flea egg control—residual ovicidal activity

Materials and Methods:

Animals: 19 healthy mongrel dogs, 7 males, 12 females from BerTek, Inc. colony, of varying ages and weights (1-7 years, and 22.2-43.5 lbs). Dogs not treated with any insecticides within one month of Day 0. Standard housing and feeding protocol for the BerTek dog colony These 19 dogs were chosen from a group of 24 (7 males, 17 females) based on pre-treatment qualification. Dogs exhibiting the best levels of flea retention and larval eclosion were chosen.

Test parasites: Cat Fleas and BDT from an in-house colony. ADT from colony at Oklahoma State.

Test insecticide treatment matches the Confidential Statement of Formula (CSF)

Design:

3 treatments: a control group (1), an insecticide treated group (2), and an insecticide treated group that was wetted once per week throughout the study (3).

Replicates: 6 dogs in control (group 1), 10 dogs in insecticide treated (group 2), and 3 dogs in insecticide treated with weekly wetting (group 3).

Randomization: Dogs were ranked by weight and then listed in that order on a random treatment group assignment table. The ten heaviest dogs were randomly

assigned to one of the three treatments and then the nine lightest dogs were randomly assigned to one of the three treatments.

Dosages: 1.5 ml for dogs weighing up to 15 lbs, 3.0 ml for dogs weighing from 16 to 30 lbs, and 6 ml for dogs weighing from 31-60 lbs. Material administered to each dog along the dorsal line in approximately 3 equal spots—one between shoulders, one in the middle of the back, one at the base of the tail. There was one application to all dogs in groups 2 and 3, with no re-treatments. Dogs from group 3 were wetted weekly starting 12 days after initial treatment using spray from a dog bathing wand—protocol says "thoroughly wetted." Wettings were done after a parasite count, but prior to the next subsequent infestation

Infestations: BDT and ADT (50 each) were applied manually to each animal 4 times: Pretreatment, 13, 20, and 27 days post treatment. Fleas (100 each) were applied manually to each animal 11 times: Pretreatment, 14, 21, 28, 34, 41, 48, 55, 62, 69, and 76 days post treatment. All parasites for each placement were placed along the dorsal midline from its head to the base of the tail. Gloves and aprons of applicators were changed between treatments to minimize contamination.

Data collection:

Ticks: 24, 48, (visual) and 72 hours after treatment (removal counting), and then 72 hours after each re-infestation (removal counting), with each scored as alive or dead

Fleas: 24 (visual) and 72 hours after treatment (removal counting) and 48 hours after each re-infestation (removal counting), with each scored as alive or dead.

Pan counts (pans beneath dogs in their cages) were also made for dead and moribund fleas/ticks falling from animals in days 1-3 (this was only for group 3 and 3 dogs from group one).

Flea egg mortality: This was assessed after the adult studies were completed on day 30. Dogs were infested weekly with fleas (100 each). Egg collection pans were placed under each animals cage and left there for 20 hours past infestation to collect eggs. Fleas were removed after each week's egg collection to maintain equal pressure. All eggs from each animal (up to 100) were collected and transferred to rearing containers labeled separately for each dog. Eggs were incubated and larval eclosion was evaluated 3-4 days later. Starting with the day 61 count, larvae were placed on rearing media and adult emergence was evaluated 35 days after initial egg collection.

Statistics: Only descriptive statistics are given. Geometric means were calculated for each group and then % control was calculated by comparing treatment means to the control. % control = ([GM ctrl – GM trt]/GM ctrl)*100

Study Summary of the Results:

RF-2042B provided >88% control of ADT and >94% control of BDT at 23 days after treatment. For fleas, >94% control of fleas from 1-23 days after treatment. By day 30, "control of all three parasites had dropped below acceptable levels (< 90%)

Inhibition of flea hatch was >88% through day 82 and inhibition of adult flea emergence was >91% through day 114.

Wetting group 3 dogs did not dramatically affect the efficacy of the treatment.

Counts of dead parasites on Days 1-3 demonstrated actual mortality of all three parasite species during the initial days following treatment

Entomologist's Observations/Discussion

Results section lists tables 2-6, but there is no table 6 in study.

With some variability, efficacy against adult ticks takes 2-3 days to exceed 80% mortality (no quick knock down) based on visual counts. This data is similar to pan count data showing no difference in the number of dead ticks in the first 3 days between 3 dogs from group one and 3 dogs from group 3. Efficacy against adult ticks exceeds 84% through day 23. There is appreciable decrease by day 30, down to about 55-60% efficacy. There were no important differences between groups 2 and 3.

Efficacy against adult fleas is acceptable from Day 1 (in both visual and pan count data) through day 23, exceeding 94%. There is appreciable decrease by day 30, down to about 55% efficacy. No difference between groups 2 and 3. There is more variability by day 23 between dogs, but overall means still show good adulticidal activity.

Ovicidal activity is acceptable from days 37 through day 79 (egg hatch inhibition greater than 92% and adult emergence inhibition greater than 86%)

The statement of "demonstrated actual mortality of all three parasite species" in the pan trap observations is not supported for fleas, and is only significant for cat fleas.

Observations/Discussion:

1. Dog qualifications were only done with fleas and not ticks. OPPTS 810.3300 indicates a tick qualification is preferred.

2. Most claims in study are well supported, but the following label claim should be changed as follows:

The claim of activity against fleas and ticks for "3 to 4 weeks" should be changed to ' 3 weeks' based on the study results, where the product controlled these pests for up to 23 days post-treatment.

3. While dogs were assigned randomly to treatment groups, it appears that the four heaviest dogs (35.6 lbs and higher) all ended up in treatment 2. This may slightly impact the claim that wetting the dogs does not affect efficacy because none of the largest dogs were placed in group 3. It would have been better to have a larger sample size for group 3 with some larger dogs, because larger dogs may have the residue more relatively diluted over their bodies, and thus wetting may have had a more significant effect.

4. With regard to wetting, the authors do not adequately describe 'thoroughly wetted.' Was a measured or approximate volume of water applied? Was it hot water or cold water? The claim of 'efficacious after rain or swimming' should be changed to 'efficacious after wetting,' because swimming was not adequately simulated in the study.

5. Number of dogs in treatment 3 (3 dogs) is well below the minimum of 6 recommended in OPPTS 810.3300. Also, 810.3300 states there should be 5 or more large dogs used in the study, and preferably at least 3 large dogs in each treatment group. This study only had 3 total large dogs, all of which were in group 2, and no 'very large' (>60 lbs) dogs in any group.

6. Titration of a.i. appears valid for the particular study, where the minimum dose works out to about 1 ml per 10 lbs of each dog to a maximum of about 2 ml per 10 pounds of dog. This worked out to 1.5 ml for dogs up to 15 lbs, 3.0 ml for dogs 15-30 lbs, and 6.0 mL for dogs 30-60 lbs. However, there were no dogs in the "very large" category (> 60 lbs.) On the label, it indicates there is an 8 ml dose for these "very large" dogs, even though they were not evaluated in this study. Therefore, the application rate for extra larger dogs should be consistent with that of smaller dogs and should be changed from 8.0 cc to 9.0 cc.

7. The parasite placement was along the dorsal midline of the animal, which is the same area where treatment was applied. This doesn't meet the standard of 'sufficient anatomical distribution' per 810.3300. It might have been better to apply the ticks/fleas to other areas of the body to avoid bias toward the most heavily coated hair, closest to where the insecticide was applied. Other studies use kennel cages where ticks are placed inside with the dog and allowed to freely infest the dog from the legs, back, head, or elsewhere, which would be a more realistic simulation of natural conditions. Please explain and justify why application of ticks and fleas were made to the mid-dorsal line where the treatment was made and why it is more appropriate for product evaluation than a random placement of parasites on different areas of the animal.

8. Other label claims.

The remaining label claims are acceptable except as noted below.

Effective on Indoor and Outdoor dogs—Not acceptable, since dogs were not exposed to outdoor conditions in any of the studies.

Aids in control of ticks for up to 30 days [one month]—Not acceptable. Should be revised to 3 weeks.

Controls reinfestation for [more than 10 weeks] up to [75 days][2.5 months]—Acceptable, if reworded to 'controls flea reinfestation'

Non-Irritating/Coat Conditioning Formula—Non-irritating is acceptable, but a coat conditioning claim might not be allowed: implied safety claim, 40 CFR 156.10.

RF2042 [CDSO] prevents flea eggs from developing into adult fleas [more than 10 weeks] for up to [75 days][2.5 months]. RF2042 [CDSO] also kills fleas and ticks for 3 to 4 weeks and kills and repels mosquitoes for 3 to 4 weeks—Not acceptable. Kills fleas and ticks for up to 3 weeks. Mosquito efficacy varied by species. Claims of 3 to 4 weeks are acceptable for *Aedes aegypti*, and *Anopheles quadrimaculatus*, but not *Culex quinquefasiatus*.

[RF2042 [CDSO] is water resistant and remains efficacious following exposure to rainfall or swimming.]—Unacceptable. Studies demonstrated water resistance, but did not adequately simulate swimming or the generic claim of 'rainfall.'