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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

12/APR/2000

MEMORANDUM

Subject: EPA Reg. No: 65331-U Frontline Plus for Cats
DP Barcodes: D261563
Case No: 066318
PC Code: 129121

From: Masih Hashim, D.V.M., Ph.D., Toxicologist MH
Byron Backus, Ph.D., Toxicologist BTB
Technical Review Branch
Registration Division (7505C)

To: Ann Sibold, PM Team 03
Insecticide Branch
Registration Division (7505C)

Applicant: Merial Limited
2100 Ronson Road
Iselin, NJ 08830

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Fipronil	9.8
S-Methoprene	12.0
Inert Ingredients	78.2
Total:	100.0

BACKGROUND: In a companion animal safety study (MRID 44942009), Fipronil/s-Methoprene solution for cats (Active Ingredients: Fipronil:10% w/v; (S)-methoprene:12% w/v) was topically applied at dose levels of 0.5 mL given at 1X , 1.5 mL at 3X, or 2.5 m at 5X (times the maximum recommended dose) to groups of 6 male and 6 female cats. Controls were not dosed. Animals were treated on Study Day 0 and again on Study Day 28. This report includes results of the study up to Day 42.

RECOMMENDATIONS: The executive summary from the DER for MRID 44942009 is given in the following pages.

FRONTLINE PLUS FOR CATS AND KITTENS

[Fipronil and (S)-Methoprene solution]
STUDY TYPE: Companion Animal Safety - Cat (OPPTS 870.7200)
MRID 44942009

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
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Disclaimer

This review may have been altered subsequent to the contractors signatures above.

Managed by Lockheed Martin Energy Research Corp., for the U.S. Department of Energy under Contract No. DE-AC05-96OR22464.

EPA Reviewer: Masih Hashim, D.V.M., Ph.D. _____ Date: _____

EPA Work Assignment Manager:John Redden, M.S._____ Date: _____
Registration Division (7505C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Cats and Kittens [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODE: D261563; MRID NUMBER: 44942009

TEST MATERIAL: Frontline Plus

STUDY NUMBER: GB011\99-001

TESTING FACILITY: Biological Laboratories Europe Ltd, Glenamoy, Ballina, County Mayo, Ireland

SPONSOR: Merial Limited, Pharmaceutical Research and Development, 2100 Ronson Road, Iselin, NJ 08830-3077

TITLE OF REPORT: Fipronil/s-Methoprene Topical Solution: Target Species Safety Study in the Cat.

AUTHOR: Dianne Clery M.V.B., Ph.D., M.R.C.V.S.

REPORT ISSUED: September 29, 1999 (Interim Final Report)

EXECUTIVE SUMMARY: In a companion animal safety study, MRID 44942009, Fipronil/s-Methoprene solution for cats (Active Ingredients: Fipronil:10% w/v; (S)-methoprene:12% w/v) was topically applied at dose levels of 0.5 mL (1X), 1.5 mL (3X) or 2.5 mL (5X times the maximum recommended dose) to groups of 6 male and 6 female kittens (52-59 days old at the initiation of the study). Controls were not dosed. Animals were treated on Study Day 0 and again on Study Day 28. The report includes results of the study up to Day 42.

The animals were observed hourly for 6 hr following each treatment, and twice daily on every study day (with the exception of Day –14 when they were observed only once). Clinical evaluations were conducted on Days –14 (or –13), on the day of each treatment (Day 0 and Day 28) and on Study Days 1, 3, 7, 14, 21, 29, 31, 35 and 42. Body weights were recorded at the start of acclimation on Study Day-14 (with the exception of 5 cats who were weighed on Day-13), prior to dosing on Study Days 0 and 28, and on Study Days –7, -1, 7, 14, 21, 35, and 42. Blood samples were obtained from the jugular vein on Study Days-4, or –3 (depending on the set) and thereafter on Days 14, 28 (before treatment) and 43.

No clinical signs of erythema, edema, alopecia or abnormal hair coat condition were observed 1-6 hr post-dosing in any of the treated animals or during any of the other observation periods from Study Day –14 to Study Day 42. Animals in all treated groups (maximum of 9 of 12 in 5X group on Study Day 28) had skin flakes and off-white material at the application site, and four in the 5X group exhibited pruritus on Days 1, 2 or 3. No ocular, muscular, cardiovascular, or behavioral changes or abnormalities of the mucus membranes were observed in the treated cats. There were no morphological abnormalities in RBCs that could be attributed to treatment.

Overall, no treatment-related, biologically-significant effects on body weight, clinical bio-chemistry, or hematology, were reported. Although there were statistically-significant changes in hematology and clinical chemistry parameters in some treatment groups at some sampling times (i.e., reduction in mean corpuscular volume; reduction in % neutrophils, increase in % mono-cytes; increase in eosinophils, increase in reticulocytes, increase in urea), none of the changes followed a clear dose-response relationship and most were within the normal reference range. Summary statistics were presented by sex for each treatment group only in those cases where a statisitically significant change was observed ($p < 0.10$). It is recommended that mean values of all hematological and clinical chemistry parameters for each sex for each treatment group and for all sampling periods be included in the final report. Because a full complement of animals was not available at the start of the study, the animals were tested in sets, and the data for each study day was collected on five separate dates (one for each set). The guidelines do not require that all the animals be treated and observed at the same time points. This interim report did not include the results of necropsies that were scheduled for Study Day 154.

This study deviated from the companion animal safety study Guidelines (OPPTS 870.7200), in that blood samples were collected prior to treatment on Days -3 or -4 and on Day 28 and not at 24 hrs following treatment, as specified by the guidelines. However, the HED Companion Animal Safety Committee suggested that this study could be classified as acceptable for the following reasons: 1) the remainder of the study was conducted according to the guidelines; 2) there was no evidence of toxicity in any of the animals; 3) as fipronil is registered at this concentration in other products, there are CAS studies with no evidence of toxicity at 5X. In addition, methoprene is used with many other chemicals in flea and tick products, and, in so far as the Committee is aware, there is no evidence that it interacts with these other chemicals, although the proposed 12% concentration in this product may be somewhat higher than that of most of the other products listed in REFS.

It is also noted that doses are not stated on the proposed label. HED concludes that the final dosages, as indicated on the label or as packaged in the applicator tubes, must be consistent with (no more than) the 1 X application rate in this study (0.5mL/kg). With this stipulation, and assuming that there are no additional adverse effects reported in the final report, the study is classified as **Acceptable/Guideline** for a companion animal safety study (OPPTS 870.7200) in cats (kittens).

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material: Frontline Plus for Cats and Kittens [Fipronil and (S)-methoprene solution for cats]
Description: Clear, straw colored viscous liquid
Lot/Batch No.: ML-2,095,988 508Q003
Active Ingredients: Fipronil 10% w/v; (S)-methoprene 12% w/v
Storage Conditions: 2-8°C; on one occasion the temperature increased to a maximum of about 14°C for approximately 48 hr.

B. Administration: Topical (spot on)

C. Vehicle and/or positive control

Vehicle: None
Positive control: none

D. Test animals

Species: Cat
Breed: Short-haired
Age and weight at study initiation: 52-59 days (average 56.2 days) for males, 0.6 – 0.9 kg; 52-59 days old (average 56.0; days) for females 0.5-0.9 kg
Source: Specific Pathogen Freee (SPF) Unit at Bilogical Laboratories Europe, Ltd: Breeding stock originated from Hill Grove Family Farm, Ltd, Minster Lovell, Oxford, OX8 5NA, England
Housing: Individually in cages approximately 1.1 m x 0.60 m x 0.75 m
Diet: Standard commercial cat food ("New Whiskas Kitten"), once daily
Water: Potable water, *ad libitum*
Environmental conditions:
Temperature: 14-28C
Humidity: 30-83%
Air changes: 10-15/hr
Photoperiod: 12 hr light/12 hr darkness
Acclimation period:13-14 days

II. STUDY DESIGN

A. In life dates

Set 1: start: March 09, 1999; end: Aug. 10, 1999
Set 2: start; April 1, 1999; end: Sept. 2, 1999
Set 3: start: April 29, 1999; end: Sept. 30, 1999

Set 4: start; June 29, 1999; end: Nov. 30, 1999
Set 5: start: July 13, 1999; end: Dec. 14, 1999

B. Animal assignment/ Dosage and Administration

The study design was a randomized block using random order numbers from Fisher and Yates tables. As it was not possible to have a full complement of animals at the start of the study, the cats were enrolled in 5 sets. Each set consisted of cats of the same age. On Day-1 for each set, replicates of four same sex cats were formed based on body weight. Animals were ranked by decreasing body weight within sex and the first four in each rank formed a replicate, the second another replicate, and so on. Across all sets a total of 12 replicates were formed, each consisting of six males and six females. Within replicates, animals were randomly allocated to one of four treatment groups. Treatments were applied as 1, 3, or 5 spots of product on the mid-point of the dorsal neck between the base of the skull and shoulder blades. The dose corresponded to 0.5 mL for Group 2 (1X), 1.5 mL for Group 3 (3X), and 2.5 mL for Group 4 (5X). Animals were dosed on Study Day 0 and again on Study Day 28.

Table 1. Experimental design

Group	No. of animals		Treatment (mL)	Dose[a] (MRD)
	Male	Female		
1	6	6	Controls	0
2	6	6	0.5	1X
3	6	6	1.5	3X
4	6	6	2.5	5X

Data taken from p. 21, MRID 44942009.
[a]Treatments were given on Day 0 and again on Day 28

C. Dose selection rationale

The rationale for dose levels was to establish the margin of safety and potential dermal and systemic toxicity of 1X, 3X, and 5X the maximum recommended dose.

D. Experimental design

Pre-treatment clinical observations were conducted on Day -14 (or Day -13) and on Day-1. Following dosing, the animals were observed hourly for 6 hr. The animals were observed twice daily for health problems except on Day –14 when they were observed only once. Clinical evaluations were conducted on Days –14 (Day –13 for five cats in set #1), on the day of each treatment (Day 0 and Day 28) prior to dosing and on Study Days 1, 3, 7, 14, 21, 29, 31, 35 and 42. Clinical evaluations included: skin reaction at the application site (erythema, edema, alopecia, hair-coat condition, and pruritus); rectal temperature; condition of the eyes; muscular disturbances (tremors, paralysis and atony); gastrointestinal disturbances (vomiting, consistency of stools); cardiovascular changes;

color of mucus membranes; and general behavior. Body weights were recorded at the start of acclimation on Study Day-14 (with the exception of 5 cats in set #1 who were weighed on Day-13), prior to dosing on Study Days 0 and 28, and on Study Days –7, -1, 7, 14, 21, 35, and 42.

E. Pathological parameters

Blood samples were obtained from the jugular vein on Study Days -4, or –3 (depending on set) and thereafter on Days 14, 28 and 42. The animals were fasted overnight prior to blood collection. 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	x	Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)*		
	(Activated partial thromboplastin time)*		
x	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*		Total Cholesterol
x	Potassium*	x	Globulin*
x	Sodium*	x	Glucose*
		x	Total and direct bilirubin*
	ENZYMES	x	Total serum protein*
x	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	x	Albunib/Globulin ratio
x	Serum alanine amino- transferase (also SGPT)*		
x	Serum aspartate amino- transferase(also SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F Statistics

Body weight data were analyzed by mixed model analysis of variance using weight on Day -1 as the covariate. Rectal temperature, clinical chemistry, and hematology data were analyzed using repeated measures of variance. For all effects p values of less than 0.10 were presented. Although tables of summary statistics were presented (Appendix 7), mean values were not presented by sex for each treatment group for each day of sampling.

G. Disposition of animals

Not reported.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 0.5 mL of product was equivalent to 50 mg fipronil and 60 mg (S)-methoprene.

B. Mortality

One cat (1X group) was found dead on May 19, 1999. The cause of death was attributed to damage to the wall of the jugular vein during blood sampling, and subsequent slow hemorrhage, hematoma formation and terminal rupture of a major blood vessel.

C. Clinical signs

Clinical observations are presented in Table 2. No signs of erythema, edema, alopecia or abnormal hair coat condition were observed in any of the treated animals 1-6 hr post-dosing or from Study Day –14 to Study Day 42. Several cats exhibited pruritus at the treatment site which may have been associated with matting of the hair due to the treatment. Throughout the study period, a variable number of cats in each treatment group were recorded as having "skin flakes" loosely attached to the skin at the base of the hairs at the treatment site, and/or with white or off-white material (made-up of pinpoint size particles) attached to hair tips at the treatment site. No ocular, muscular, cardiovascular, or behavioral changes or abnormalities of the mucus membranes were observed in the treated cats. Although rectal temperature of some control and treated cats were outside the normal range, there was no significant effect of treatment on this parameter. Ataxia and incoordination were observed in two animals in the control group, but in none of the treated animals.

TABLE 2. Clinical observations of cats treated with Fipronil/S-Methoprene topical solution			
Treatment group	**Sex**	**Day**	**Observation**
Control	F	0	Fecal staining in 1 cat
	F	28	Signs of ataxia and incoordination of the hind limbs in 1 cat
	M	42	Signs of ataxia and incoordination of the hind limbs in 1 cat
1X Treatment	M,F	0-31	Off-white material at test site in 2/12 on Day 0; 2/12 on Day 1; 0/12 on Day 3; 1/11 on Day 28; 0/11 on Day 29; 0/11 on Day 31.
3X- Treatment	F	0	Slight pruritus at the treatment site in 1 cat
	M,F	0-31	Off-white material at test site in 3/12 on Day 0; 6/12 on Day 1; 2/12 on Day 3; 4/12 on Day 28; 5/12 on Day 29; 0/12 on Day 31
	M	7	Fecal staining in 1 cat
5X- Treatment	M	0	Slight pruritus at the treatment site in 2 cats
	M	1	Slight pruritus at the treatment site in 2 cats
	M	3	Slight pruritus at the treatment site in 1 cat
	M.F	0-31	Off-white material at test site in 5/12 on Day 0; 6/12 on Day 1; 4/12 on Day 3; 9/12 on Day 28; 6/12 on Day 29; 1/12 on Day 31

Data taken from pp. 31-33, and Table 32, p. 84, MRID 44942009.

D. Bodyweight and weight gain

Between Study Day 0 and Day 42 all cats gained weight. On Study Day 42 males in the treated groups showed a significant increase in body weight compared to controls. On Days 7, 14, 21, 28, and 35 some of the treated groups had a higher mean body weight than controls.

E. Food consumption

Food consumption was not reported.

F. Hematology

It was reported that no significant effect of treatment was observed on white blood count, red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration, platelet number, lymphocytes, basophils, or prothrombin time. Statistically significant changes were observed in percent neutrophils, percent monocytes, percent eosinophils and number of reticulocytes (see Table 3).

Table 3. Statistically significant changes in hematology parameters treated with Fipronil/S-Methoprene topical solution [a]								
	Males				Females			
Parameter	controls	1X	3X	5X	controls	1X	3X	5X
% Neutrophils	56.29	58.00	56.58	57.46	59.33	57.41	58.62	56.38[b]
% Monocytes	3.20	3.04	3.20	3.08	2.67	3.22[c]	3.04[d]	3.25[e]
% Eosinophils	5.29	4.17[f]	4.83	4.91	4.17	5.45[f]	4.79	4.63
RETIC (per 1000 RBC)	4.92	8.42[b]	9.46[g]	6.54	6.38	4.50	5.50	4.63

Data taken from Table 7, p. 124, MRID 44942009

[a] Mean values

[b] $p<0.04$

[c] $p<0.012$

[d] $p<0.08$

[e] $p<0.01$

[f] $p<0.02$

[g] $p<0.009$

In female cats assigned to the 5X group there was a statistically significant ($p<0.04$) reduction in % neutrophils (mean 56.38 ±3.21%) compared to controls (59.33 ±5.04) on Day 42); however, the values were within the normal range of reference values for this parameter (52-71%) and, therefore, were not considered to be biologically significant. Statistically significant increases were also observed in % monocytes in females in the 1X group (3.22% ±0.69%; $p<0.012$,), the 3X group (3.04% ±0.91%; $p<0.08$), and the 5X group (3.25% ±0.68%; $p<0.01$) when compared to controls (2.67% ±0.70%). All were within the range of reference values for this parameter (1% to 4%). Eosinophils decreased in males in the 1X group (4.17% ±0.96% vs. 5.29% ±1.87% in controls; $p<0.08$) and increased in the 1X females (5.45% ±2.08% vs. 4.17% ±0.96% in the female controls; $p<0.02$). Reported reference values ranged from 1 to 12%. Reticulocytes increased significantly in male cats in the 1X group (8.42±4.21/1000 RBC; $p<0.04$) and in the 3X group (9.46 ±4.73/1000 RBC; $p<0.009$) as compared to controls (4.92±2.15/1000 RBC). The reported range of reference values for this parameter is 2-17/1000 RBC.

Hematological data for 1 animal in the 1X group on Study Day 14, 3 animals each in control and all treated groups on Study Day 28 and 1 animal in the 3X group on Study Day 42 were excluded from statistical analysis. It was reported that these data were physiologically invalid because of associated low HCT and high HGB values. RBC values were also low. It was stated that these abnormal values may "indicate a sample problem such as hemolysis" (no other explanation was given).

On Study Day 42 cats from set 5 assigned to all study groups (controls and treatment groups) exhibited high WBC values (range 22.1 to 68.8 x $10^3/\mu L$ vs. range of reference values of 5.6-23.4 x $10^3/\mu L$). An apparent reduction in mean corpuscular volume was seen on Study Day 14 in the 1X group (mean value of 48.30 ±2.28 fl; $p<0.03$) and 5X group (48.62 ±3.19 fl; $p<0.04$) as compared to controls (51.66 ±4.73 fl).

Morphological abnormalities were seen in red blood cells of control and treated cats. These consisted primarily of anisocytosis and poikilocytosis which were considered to be common occurrences in the cat colony of the test laboratory.

G. Clinical chemistry

Mean values for each parameter for each sex in each treatment group and for each sampling time were presented only in those cases where there were statitistically significant changes. Overall mean values for both sexes, combined for all sampling times, were presented, as were overall mean values for each sampling day. It was reported that no significant effect of treatment was observed on ALP, ALT, AST, creatinine, total protein, albumin, globulin, albumin/globulin ratio, total bilirubin, glucose, sodium, potassium, chloride, calcium, or phosphorus. Cats assigned to the 3X group exhibited a statistically significant increase ($p<0.01$) in urea (mean value of 10.62 ±2.26 mmol/L vs. 8.63 ±2.08 mmol/L in controls). Reference values for this parameter ranged from 1.29-14.35 mmol/L. Total bilirubin values for eight set 1 cats (all test groups) and one set 5 cat (control group) for Study Day –3/–4 were excluded from statistical analysis because the control run values were abnormally high, and the run was not repeated.

H. Necropsy findings

Necropsy was performed on the one cat that died during the study. A large hematoma was found subcutaneously in the neck, extending around the trachea and esophagus and into the anterior of the thoracic cavity. There appeared to be damage to the wall of the right jugular vein. The carcass and all major organs were very pale. The remaining cats were scheduled to be necropsied on Day 154.

IV. DISCUSSION

Groups of 6 male and 6 female kittens (52-59 days old at study initiation) were treated topically with 0.5, 1.5 or 2.5 mL of Frontline Plus (1, 3 or 5 times the MRD; active ingredients: Fipronil:10% w/v; (S)-methoprene:12% w/v). Each 0.5 mL of product was equivalent to 50 mg fipronil and 60 mg (S)-methoprene. Controls were not dosed. Animals were treated on Day 0 and again on Day 28.

One animal died during the study. The death was attributed to damage to the jugular vein during blood sampling. Clinical evaluation of the treated animals revealed no treatment related effects; there were no clinical signs of erythema, edema, alopecia or abnormal hair

coat condition at the treatment site, and no ocular, muscular, cardiovascular, or behavioral changes or abnormalities of the mucus membranes were observed in the treated cats. Animals in all treated groups (maximum of 9 of 12 in the 5X group on Study Day 28) had skin flakes and off-white material at the application site, and four in the high-dose group exhibited pruritus on Days 1, 2 or 3. The pruritus may have been associated with matting of the hair due to the treatment.

Overall, no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology, were reported. Although statistically-significant changes in hematology and clinical chemistry parameters occurred in some treatment groups at some sampling times (i.e., reduction in mean corpuscular volume; reduction in % neutrophils, increase in % monocytes; increase in eosinophils, increase in reticulocytes, increase in urea), none of the changes followed a clear dose-response relationship and most were within the normal reference range. Summary statistics were presented by sex for each treatment group only in those cases where a statisitically significant change was observed ($p<0.10$). It is recommended that mean values of all hematological and clinical chemistry parameters for each sex for each treatment group and for all sampling periods be included in the final report. Because the total number of animals was not available at the initiation of the study, the animals were tested in sets, and the data for each study day was collected on five separate dates (one for each set). Although this is not a standard experimental protocol, the guidelines do not require that all the animals be treated and observed at the same time points. This interim report did not include the results of necropsies that were scheduled for Study Day 154.

This study deviated from the companion animal safety study Guidelines (OPPTS 870.7200), in that blood samples were collected prior to treatment on Days -3 or -4 and on Day 28 and not at 24 hrs following treatment, as specified by the guidelines. However, the HED Companion Animal Safety Committee suggested that this study could be classified as acceptable for the following reasons: 1) the remainder of the study was conducted according to the guidelines; 2) there was no evidence of toxicity in any of the animals; 3) as fipronil is registered at this concentration in other products, there are CAS studies with no evidence of toxicity at 5X. In addition, methoprene is used with many other chemicals in flea and tick products, and, in so far as the Committee is aware, there is no evidence that it interacts with these other chemicals, although the proposed 12% concentration in this product may be somewhat higher than that of most of the other products listed in REFS.

It is also noted that doses are not stated on the proposed label. HED concludes that the final dosages, as indicated on the label or as packaged in the applicator tubes, must be consistent with (no more than) the 1 X application rate in this study (0.5mL/kg). With this stipulation, and assuming that there are no additional adverse effects reported in the final report, the study is classified as **Acceptable/Guideline** for a companion animal safety study (OPPTS 870.7200) in cats (kittens).