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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: October 3, 2005

MEMORANDUM

Subject: EPA File Symbol: 80490-G PROMERIS SPOT ON FOR CATS
DP Barcode: D314413
Decision No.: 354816
PC Code: 281250 [Metaflumizone; R 28153; BAS 320 I]

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

To: Ann Hanger/John Hebert RM 07
Insecticide Branch
Registration Division (7505C)

Registrant: FORT DODGE ANIMAL HEALTH

FORMULATION DECLARATION FROM LABEL:

	% by wt
Active Ingredient(s):	
Metaflumizone [R-28153; BAS 320 I] (CAS #139968-49-3)*	18.53%
Inert Ingredients:	81.47%
Total:	100.00%

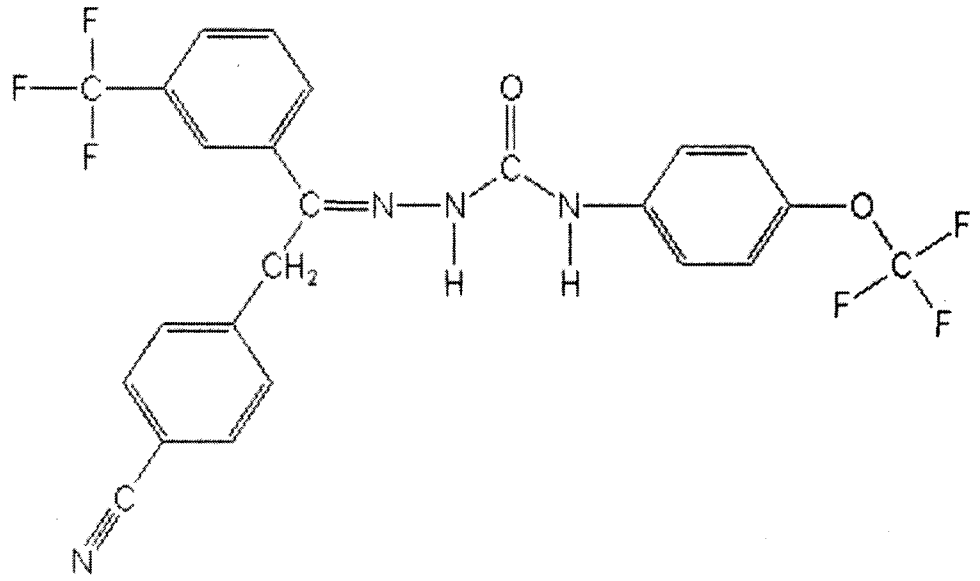
*According to the proposed label the CAS No. is 35037-73-1; however, other references give a CAS #139968-49-3

ACTION REQUESTED:

"Please review the animal safety data (MRIDs 46437615 and 46437616) submitted for this 18.53% metaflumizone (aka BAS 320I) product claiming control of fleas on cats and kittens over 8 weeks."

BACKGROUND:

This proposed product contains the new active Metaflumizone (also known as R 28153; BAS 320 I), with the following structure:



The use of Metaflumizone as an active in a formulation to kill and/or control fleas on cats and kittens is a new use.

This package includes companion animal safety studies on adult cats (MRID 46437615) and 8-week old kittens (MRID 46437616).

COMMENTS AND RECOMMENDATIONS:

1. Both the adult cat (MRID 46437615) and kitten (MRID 46437616) companion animal safety studies have been classified as acceptable, and both demonstrate an adequate 5X margin of safety for most of the proposed uses of this formulation as a once-a-month spot-on for cats and kittens.

2. Because none of the kittens in this study weighed over 9 lbs (approximately 4 kg) the single-dose application amount to kittens from 8 weeks of age to 6 months should be limited to 0.8 mL.

3. As it was not demonstrated that ingestion alone was responsible for the salivation, the proposed label statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." should be revised to something like: "Exposure or ingestion may result in temporary salivation; this response should disappear without treatment." The claim that the salivation is not a sign of toxicity is not adequately supported by data, and could also be interpreted as an inappropriate safety claim (refer to CFR 40 §156.10(a)(5)(ix)).

4. The following is the executive summary from the adult cat (MRID 46437615) study:

In a companion animal safety study (MRID 46437615), 4 groups, each containing 12 (6/sex) young (173-245 days old) adult cats (source: Liberty Research Inc., Waverly, NY; males: 2.2 to 4.5 kg; females: 1.88-3.05 kg) were treated at 0X (4.0 or 8.0 mL placebo), 1X (0.8 or 1.6 mL spot-on formulation), 3X (2.4 or 4.8 mL spot-on formulation) and 5X (4.0 mL or 8.0 spot-on formulation; the lower doses were for cats weighing less than 4 kg, while the higher doses were for cats weighing more than 4 kg; one male and no females in each group weighed more than 4 kg). Application to each cat was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the syringe was dragged back slowly distally.

According to proposed label directions the product would be applied as a spot-on with a dosage rate of 0.8 mL for cats $\leq$ 4 kg and 1.6 mL for cats >4 kg.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Cats were individually weighed on Days -15, -8, -1, and then postdose on Days 7, 14, 21 and 28. Food consumption is reported (g/cat/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (about 24 hours postdose), 8 and 22.

All cats survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of cats (including some in the placebo group) from 15 minutes postdose and continuing through 2 hours postdose with the following incidences: placebo control: 2/6M, 3/6F; 1X: 1/6M, 2/6F; 3X: 0/6M, 2/6F; 5X: 2/6M, 1/6F. Salivation was also seen in a 1X male at the physical examination on Day 1 (day of dosing) and in a 5X female on Day 2. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

One 3X female (#121) had a drop in platelet count on Day 8 with a recovery on Day 22 (Pretest: 477 K/mm^3; 24 hrs: 325 K/mm^3; Day 8: 83 K/mm^3; Day 22: 219 K/mm^3). However, this was an isolated case, as a similar effect was not observed in any of the other cats.

Activated Partial Thromboplastin Time (APTT) was somewhat increased in all groups (including Placebo Controls) at 24 hrs and 8 Days. For combined sexes the following mean values were obtained at 24 hours postdose (pretest values = 1.00): Placebo Control: 1.27; 1X: 1.32; 3X: 1.36; and 5X: 1.27. Corresponding values on Day 8 were: Placebo Control: 1.19; 1X: 1.27; 3X: 1.30; 5X: 1.16. Day 22 and predose values were essentially the same. In the absence of any indication of a dose-related trend, it is doubtful that this finding is associated with exposure to either the active or inerts in this formulation. In addition, the degree of elevation is biologically non-significant.

Mean eosinophil counts were significantly increased in males relative to their controls on Day 8, values (with controls = 1.00) were: 1X: 2.45; 3X: 1.58; 5X: 2.97. However, this was not concurrently observed in females, as their corresponding group values relative to the control were: 1X: 0.59; 3X: 0.83; 5X: 0.70. Also, the relatively high

mean value for 5X males on Day 8 was largely due to a single high value in one cat (#141: value 9.02 x 10^3/µL), and the mean value for the remaining 5 males in this group was 1.05 (range: 0.65-1.53) x 10^3/µL (1.05 x 10^3/µL = 1.31X the concurrent control value). The value for cat #141 had dropped to a more normal 1.19 x 10^3/µL by Day 22. This temporary eosinophilia was probably spontaneous in nature (it may have involved an immune response to intestinal parasites).

Sporadic statistically significant changes involving clinical chemistry parameters (total bilirubin, globulin, creatinine) in gender-pooled samples or in one sex were not biologically relevant, as they were minimal and individual values fell within normal ranges.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for adult cats, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation in adult cats. While salivation was noted (mostly in the 2-hour period following application) this was probably associated with ingestion from grooming and/or the odor and/or taste of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Exposure or ingestion may result in temporary salivation; this response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

5. The following is the executive summary from the 8-week-old kitten (MRID 46437616) study:

In a companion animal safety study (MRID 46437616), 4 groups, each containing 12 (6/sex) 53-57 day-old kittens (source: Liberty Research Inc., Waverly, NY; weights on Day -1: males: 0.568 to 0.866 kg; females: 0.566 to 0.855 kg) were treated at 0X (4.0 mL placebo), 1X (0.8 mL spot-on formulation), 3X (2.4 mL spot-on formulation) and 5X (4.0 mL spot-on formulation). Application to each kitten was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the dispensing syringe was dragged back slowly distally.

According to proposed label directions the product would be applied as a spot-on with a dosage rate of 0.8 mL for cats and kittens $\leq$ 4 kg and 1.6 mL for cats >4 kg.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Kittens were individually weighed on Days -14, -12, -9, -7, -5, -2, -1, and then postdose on Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 and 29. Food consumption is reported (g/kitten/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (24 hours postdose), 8 and 22. If redraws were necessary these were collected approximately 48 hours after the initial draws.

All kittens survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of kittens (including some in the placebo group) at 1 hour postdose with the following incidences: placebo

control: 3/6M, 2/6F; 1X: 0/6M, 0/6F; 3X: 1/6M, 1/6F; 5X: 1/6M, 3/6F. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

Sporadic statistically significant differences involving hematology and clinical chemistry parameters (leukocyte counts, MCHC, prothrombin time, alkaline phosphatase activity, potassium and chloride) in gender-pooled samples or in one sex were not biologically relevant, as they were not exposure/dose-related, were generally minimal, and individual values tended to fall within normal ranges. Similar changes in the same parameters were not observed in the adult cat study (MRID 46437615) with this formulation.

As no kittens weighing more than 4 kg were tested in this study, labeling should indicate that no more than 0.8 mL should be applied to kittens up to 6 months of age.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for 8-week-old kittens, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation at an application of rate of 0.8 mL/dose. While salivation was noted (in the 2-hour period following application) this may have been associated with ingestion from grooming and/or the odor and/or taste [possibly from dermal absorption] of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Exposure or ingestion may result in temporary salivation; this response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

EPA Primary Reviewer: Byron T. Backus, Ph.D. **Signature:** _____
Technical Review Branch, Registration Division (7505C) **Date** _____
EPA Secondary Reviewer: John Redden, M.S. **Signature:** _____
Technical Review Branch, Registration Division (7505C) **Date** _____

DATA EVALUATION RECORD

STUDY TYPE: **Companion Animal Safety - Adult Cats (OPPTS 870.7200)**

PC CODE: 281250 (Metaflumizone; R-28153)

DP BARCODE: D314413 **RISK MANAGER: (EPA): 07** **DECISION NO.: 354816**

PRODUCT AND TEST MATERIAL: 20% w/v R-28153 spot-on formulation, Lot No. 0381704, a pale yellow liquid with a specific gravity of 1.085 g/mL containing (from p. 429 of MRID 464376-15) 20.3% R-28153 (Metaflumizone).

CITATION: Lindahl, R.G. (2004) Safety Evaluation Study of a Topically Applied Spot-On Formulation of R-28153 in Adult Cats. Study No. 817-009; Sponsor Study No. 0817-F-US-01-03. Unpublished study prepared by MPI Research, Inc. 54943 North Main St. Mattawan, MI 49071-9399. Study Completion Date: 19 May 2004. MRID 46437615.

SPONSOR: Fort Dodge Animal Health, PO Box 5366, Princeton, NJ 08543-5366.

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46437615), 4 groups, each containing 12 (6/sex) young (173-245 days old) adult cats (source: Liberty Research Inc., Waverly, NY; males: 2.2 to 4.5 kg; females: 1.8-3.5 kg) were treated at 0X (4.0 or 8.0 mL placebo), 1X (0.8 or 1.6 mL spot-on formulation), 3X (2.4 or 4.8 mL spot-on formulation) and 5X (4.0 mL or 8.0 spot-on formulation; the lower doses were for cats weighing less than 4 kg, while the higher doses were for cats weighing more than 4 kg; one male and no females in each group weighed more than 4 kg). Application to each cat was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the syringe was dragged back slowly distally.

According to proposed label directions the product would be applied as a spot-on with a dosage rate of 0.8 mL for cats $\leq$ 4 kg and 1.6 mL for cats >4 kg.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Cats were individually weighed on Days -15, -8, -1, and then postdose on Days 7, 14, 21 and 28. Food consumption is reported (g/cat/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (about 24 hours postdose), 8 and 22.

All cats survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of cats (including some in the placebo group) from 15 minutes postdose and continuing through 2 hours postdose with the following incidences: placebo control: 2/6M, 3/6F; 1X: 1/6M, 2/6F; 3X: 0/6M, 2/6F; 5X: 2/6M, 1/6F. Salivation was also seen in a 1X male at the physical examination on Day 1 (day of dosing) and in a 5X female on Day 2. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

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Activated Partial Thromboplastin Time (APTT) was somewhat increased in all groups (including Placebo Controls) at 24 hrs and 8 Days. For combined sexes the following mean values were obtained at 24 hours postdose (pretest values = 1.00): Placebo Control: 1.27; 1X: 1.32; 3X: 1.36; and 5X: 1.27. Corresponding values on Day 8 were: Placebo Control: 1.19; 1X: 1.27; 3X: 1.30; 5X: 1.16. Day 22 and predose values were essentially the same. In the absence of any indication of a dose-related trend, it is doubtful that this finding is associated with exposure to either the active or inerts in this formulation. In addition, the degree of elevation is biologically non-significant.

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Sporadic statistically significant changes involving clinical chemistry parameters (total bilirubin, globulin, creatinine) in gender-pooled samples or in one sex were not biologically relevant, as they were minimal and individual values fell within normal ranges.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for adult cats, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation in adult cats. While salivation was noted (mostly in the 2-hour period following application) this was probably associated with ingestion from grooming and/or the odor and/or taste of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Exposure or ingestion may result in a brief period of salivation; this response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

COMPLIANCE: Signed and dated Quality Assurance (p. 8), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: 20% w/v R-28153 Spot-on, with a label declaration of 18.53% Metaflumizone (also known as BAS 320 I). According to a certificate of analysis on p. 429 of MRID 46437615 the test formulation contained 20.3% (average of 6 vials) w/w R-28153 and had a specific gravity of 1.085 g/mL.
   Description: Clear yellow liquid
   Lot No.: 0381704 (manufactured November 5, 2003)
   Storage: Room Temperature, with protection from light

   Placebo: 0% w/v R-28153 Placebo. This formulation assayed 0.00% w/v R-28153. The specific gravity is reported as 1.031.
   Description: Clear light yellow liquid
   Lot No.: 0381703 (manufactured November 3, 2003)
   Storage: Room Temperature, with protection from light

2. Administration: Topical (spot-on) on Day 1

3. Test animals
   Species: Cat
   Breed: Not indicated
   Ages and weights at study initiation (Day 1, day of dosing): Males: 5 months, 20 days to 7 months, 2 days (173 -216 days); 2.2 to 4.5 kg; Females: 5 months, 25 days to 8 months (178-245 days); 1.8 to 3.5 kg. Cats were born between May 20, 2003 and July 31, 2003.
   Source: Liberty Research Inc., Waverly, New York
   Housing: individual in stainless steel cages, each with a resting board and litter box.
   Diet: Lab Diet Laboratory Feline Diet, *ad libitum*
   Water: Tap water, *ad libitum*
   Environmental conditions:
      Temperature: 17.8° -28.9°C
      Humidity: 30 - 70%
      Air changes: not stated
      Photoperiod: approximately 12 hours light/day
   Acclimation period: 2 weeks

II. STUDY DESIGN

A. IN LIFE DATES

From the report: Application: January 20, 2004; study completion date: May 19, 2004.

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 12 (6 male, 6 female) cats per dosage group. Cats in the placebo control group were treated at with 4.0 or 8.0 mL placebo formulation, at 1X with 0.8 or 1.6 mL spot-on formulation, at 3X with 2.4 or 4.8 mL spot-on formulation and at 5X with 4.0 mL or 8.0 spot-on formulation; the lower doses were for cats weighing less than 4 kg, while the higher doses were for those weighing more than 4.0 kg (one male and no females in each group weighed more than 4 kg). Application to each cat was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the syringe was dragged back slowly distally.

From p. 14 of MRID 46437615: "The test and placebo control substances were administered once on Day 1 (January 20, 2004) by topical application. The animal was held in a position such that the surface to be treated was easily accessible. A section of hair between the shoulder blades on the dorsal midline extending cranially and caudally was separated. A plastic Becton Dickinson disposable syringe containing the appropriate

amount of test substance was placed through the hair to the skin and the test substance was applied by dragging the syringe back slowly distally along the dorsal midline, while applying the dose. Due to varying dose volumes, a 1 mL syringe was used to administer the part of the dose that was less than 1 mL. A 5 mL syringe was used for the parts of the dose volumes at 1, 2 or 4 mL. Care was taken when applying the test substance to reduce the chance of run-off, and no run-off was observed. Separate syringes were used to apply test and control substances to the animals, and gloves were changed between test and control substance application..."

TABLE 1. Study design

Group & Weight Range (kg)		Number of cats		Cumulative Dose/cat			
		Male	Female	Total/Cat	Mean Cat Wt ± S.D. (kg)	Mean mg/kg	Mean Dosage Metaflumizone (mg/kg)[a]
Placebo Control	<4.0	5	6	4.0 mL[a] 4124 mg[b]	3.4 ± 0.3 (M) 2.9 ± 0.3 (F) 3.1 ± 0.4 (C)	1213(M)[b] 1422(F)[b] 1330(C)[b]	0(M) 0(F) 0(C)
	>4.0	1	0	8.0 mL[a] 8248 mg[b]	4.1	2012[b]	0(M)
1X	<4.0	5	6	0.8 mL[c] 868 mg[c,d]	3.2 ± 0.6 (M) 2.9 ± 0.6 (F) 3.0 ± 0.6 (C)	271[d](M) 299[d](F) 289[d](C)	55.0 (M) 60.7 (F) 58.7 (C)
	>4.0	1	0	1.6 mL[c] 1736 mg[c,d]	4.4 (M)	395[d](M)	80.2 (M)
3X	<4.0	5	6	2.4 mL[c] 2604 mg[c,d]	3.4 ± 0.3 (M) 2.9 ± 0.2 (F) 3.1 ± 0.4 (C)	766[d](M) 898[d](F) 840[d](C)	155.5(M) 182.3(F) 170.5(C)
	>4.0	1	0	4.8 mL[c] 5208 mg[c,d]	4.5	1157[d](M)	234.9(M)
5X	<4.0	5	6	4.0 mL[c] 4340 mg[c,d]	3.4 ± 0.3 (M) 2.9 ± 0.4 (F) 3.2 ± 0.4 (C)	1276[d](M) 1497[d](F) 1356[d](C)	259.1(M) 303.9(F) 275.3(C)
	>4.0	1	0	8.0 mL[c] 8680 mg[c,d]	4.1	2117[d](M)	429.8(M)

Data calculated from information on p. 483-486 of MRID 46437615.
[a] Placebo
[b] Based on a specific gravity for the placebo of 1.031 g/mL (see p. 430 of MRID 46437615).
[c] Test material (with actives); amount delivered.
[d] Based on a specific gravity for the test material of 1.085 g/mL (see p. 429 of MRID 46437615)
[e] Based on 20.3% active ingredient (see p. 429 of MRID 46437615) for the test formulation.

C. DOSE SELECTION RATIONALE

From p. 14 of MRID 46437615: "The target minimum dose is 40 mg/kg. Each mL contains 200 mg R28153. Since the intended product package is for animal weight bands (≤4 kg at 0.8 mL; >4 kg at 1.6 mL), the test substance was administered at the same volume for each animal within the specified weight range. The dose levels were selected by the Sponsor to evaluate the safety of the test substance at up to five times the proposed *ad usum* rate in adult cats. This was considered to provide an appropriate safety margin for the planned therapeutic dose."

According to the proposed label this product will be packaged as 6-packs of monthly unidose applicators with the following single dosages: 0.8 mL (for cats up to 9 lb) and 1.6 mL (for cats weighing more than 9 lb). Application directions include a specification to apply the entire content of an applicator tube to the cat's skin and not to apply to the surface of the cat's fur.

D. EXPERIMENTAL DESIGN

From p. 15 of MRID 46437615: "Clinical examinations were conducted twice daily, approximately four hours apart, during the last four days of the acclimation period and continuing through the course of the study, except on days that neurological and physical examinations were conducted (Days -1, 2, 8, and 22). On those days, clinical findings were conducted once a day. On the day of dosing (Day 1), clinical examinations were made predose, 15 minutes postdose, and 1, 2, and 3 hours postdose..."

Individual body weights were measured and recorded on the day of arrival (Day -15, -8, -1 (the day before dosing) and weekly thereafter.

Individual food consumption was measured daily and reported weekly (beginning the last four days of the acclimation period and continuing through to the end of the study).

E. PATHOLOGICAL PARAMETERS

Blood samples were collected from each cat once pretest (Week -1), and on Days 2 (approximately 24 hours postdose), 8 and 22 by jugular venipuncture following an overnight fast. 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	Punctate reticulocytes
	Blood clotting measurements	X	Aggregate reticulocytes
	(Thromboplastin time)	X	Percent reticulocytes
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		

*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*	X	Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total bilirubin (T Bil)*
	ENZYMES		Direct bilirubin (D Bil)*
X	Alkaline phosphatase(ALPor ALK)*	X	Total serum protein (TP)*
	Cholinesterase(ChE)		Triglycerides
X	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	X	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)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

A statistical summary report is found in Appendix M, pages 1128 to 1134 of MRID 46437615. From p. 16 of MRID 4643615: "Each of the four treatment groups contained one animal from each of six blocks for each sex. Data were summarized, in tabular form, for each group by mean, standard deviation, number of animals examined, minimal value, and maximum value."

For body weight: "Statistical analysis was performed on body weight change at Weeks 1, 2, 3, and 4 using the PROC MIXED procedure in SAS with treatment, sex and treatment by sex as fixed effects. First the treatment by sex interaction was tested at the 5% level of significance. If the treatment by sex interaction was found significant, then the treated groups' LSMeans were compared to the control group LSMean for each sex by the 2-sided Student's t-test at the 10% level for that parameter. If the treatment by sex interaction was found not to be significant and treatment effect was found to be significant at the 10% level, treated groups' LSMeans were compared with LSMean of the control group by the 2-sided Student's t-test at the 10% level. If treatment by sex interaction, and treatment effect were found not significant for a parameter, no further analysis for that parameter was done at this step and treatments were considered to have no effect on body weight change."

For body weight and food consumption: "A repeated measure analysis was performed on body weight and food consumption parameters using the PROC MIXED procedure in SAS. The model contained pretreatment Day -1 body weight and Week -1 average food consumption values as corresponding covariates, and treatment, treatment by sex, week, sex by week, treatment by sex by week, and treatment by week as the fixed effects with week as the repeated fix effect... If treatment by sex by week interaction was found significant at the 5% level for a parameter, no further analysis was done for that parameter... If treatment by sex by week interaction was found not significant for a parameter, then treatment by sex interaction was tested at the 5% level of significance and treatment by week interactions...was tested at the 10% level for that parameter. If treatment by sex interaction was found significant for the parameter, then the treated groups' LSMeans were compared to the control group LSMeans for each sex by the 2-sided Student's t-test at the 10% level..."

From p. 18: "For all the quantitative hematology, coagulation and clinical chemistry parameters, pretreatment measurements were considered covariant in the analysis. For count data such as leukocyte count, etc., log-transformation was used. The individual parameters were analyzed by time (i.e. 24 hours postdose, Days 8 and 22) for hematology, coagulation and clinical chemistry parameters by the PROC MIXED procedure with pretreatment measurements as corresponding covariates, and treatment, sex and treatment by sex as fixed main effects and interaction..."

G. DISPOSITION OF ANIMALS

From p. 16 of MRID 46437615: "The animals were euthanized via sodium pentobarbital injection on February 17, 2004..." 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. 8], [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. Cats in the placebo control group received either 4.0 or 8.0 mL of the placebo formulation (the regular formulation less 20.3% R-28153). As a result, they received an approximately 5.96x dose of the "other ingredients" that the 1X group received. Cats in the 1X group received either 0.8 (cats<4 kg) or 1.6 mL (cats>4 kg) formulated product; those in the 3X group received either 2.4 (<4 kg) or 4.8 (>4 kg) mL formulated product, while those in the 5X group received either 4.0 (<4 kg) or 8.0(>4.0 kg) mL formulated product.

B. MORTALITY

There was no mortality, with all cats surviving the 28-day observation period.

C. CLINICAL SIGNS

It is stated (p. 20 of MRID 46437615) that: "The only observation noted was salivation, which was seen beginning 15 minutes postdose and continuing through 2 hours postdose on Day 1. This observation was noted in both sexes and across all groups, including the Placebo Controls. As salivation was noted in the Placebo Controls at a similar frequency as the treated groups, it was not considered an effect of treatment with the active ingredient R-28153."

TABLE 2. Incidences of Salivation Observed in Cats Treated with R-28153 Spot-on In the Period Immediately Following Treatment[a]				
Observation	**Placebo (Vehicle) Control**	**1X**	**3X**	**5X**
Salivation at 15 minutes postdose	1[b]/6M; 3[b]/6F	0/6M; 2[b]/6F	0/6M; 2[b]/6F	2[b]/6M; 0/6F
Salivation at 1 hr postdose	1[c]/6M; 0/6F	1[c]/6M; 1[c]/6F	0/6M; 0/6F	1[c]/6M; 1[c]/6F
Salivation at 2 hrs postdose	0/6M; 0/6F	0/6M, 0/6F	0/6M, 1[d]/6F	0/6M, 0/6F
Salivation at 15 minutes or 1 hr or 2 hrs postdose	2/6M; 3/6F	1/6M; 2/6F	0/6M; 2/6F	2/6M; 1/6F

[a]Data taken from Appendix D, Section C, pp. 454-473 of MRID 46437615.

[b]The following cats had salivation at 15 minutes: males: placebo group: 143; 1X: none; 3X: none; 5X: 102, 136; females: placebo group: 115, 131, 139; 1X: 106, 137; 3X: 108, 147; 5X: none

[c]The following cats had salivation at 1 hour postdose: males: placebo group: 119; 1X: 133; 3X: none; 5X: 102; females: placebo group: none; 1X: 106; 3X: none; 5X: 107.

The following cats had salivation at 2 hours postdose: males: placebo group: none; 1X: none; 3X: none; 5X: none; females: placebo group: none; 1X: none; 3X: 108; 5X: none.

None of the cats had salivation at 3 hours postdose.

The statement is made (p. 443 of MRID 46437615) that: "Salivation was not seen in any of the cats listed above beyond the day of dosing." However, on p. 21 it is stated (with respect to physical and neurological examinations) that: "Salivation was noted for one male at 1X and one female at 5X on Days 1 and 2, respectively." From information on p. 526 the 1X male with salivation at the physical examination on Day 1 was #133 [this cat had also shown salivation at 1 hour postdose]; from p. 531 the 5X female showing salivation on Day 2 was #122 (salivation had not been observed in this female on the Day 1 physical examination or in the 15-minute to 3-hour period following application).

From p. 21 of MRID 46437615: "Other observations noted during physical examinations (decreased skin elasticity, dehydration, increased activity, and abrasion [of the nose and muzzle]) were noted prior to as well as after treatment with the active ingredient R-28153 spot-on formulation and are common findings in cats of this age. Neurological examinations were within normal parameters at all examination intervals." This statement is consistent with the individual physical examination findings reported on pp. 525-534.

D. NEUROLOGICAL EXAMINATIONS

From p. 21: "Neurological examinations were within normal parameters at all examination intervals." This statement is consistent with the individual neurological examination findings reported in Appendix H Section C [pp. 537-632 of MRID 46437615].

E. BODY WEIGHT AND WEIGHT GAIN

From p. 20 of MRID 46437615: "Body weight was unaffected by treatment with R-28153 spot-on formulation. All animals maintained or gained weight during the study interval. Body weight was decreased to a significant level in males at 1X on Days 7 and 21 but was attributed to one small male in the group rather than an overall treatment effect. Body weight was also decreased in females at 5X on Day 7 but the decrease was less than 3% and not considered toxicologically significant."

TABLE 3. Mean Body Weights for Cats by Group					
Group	kg ± S.D.				
	Day -1	Day 7	Day 14	Day 21	Day 28
Control Males	3.53 ± 0.39	3.67 ± 0.39	3.80 ± 0.39	4.03 ± 0.40	4.17 ± 0.35
Control Females	2.90 ± 0.33	2.98 ± 0.30	3.00 ± 0.30	3.05 ± 0.28	3.07 ± 0.31
1X Males	3.42 ± 0.75	3.47* ± 0.73	3.62 ± 0.81	3.78* ± 0.87	3.97 ± 0.90
1X Females	2.85 ± 0.57	2.88 ± 0.50	3.00 ± 0.48	3.05 ± 0.45	3.10 ± 0.46
3X Males	3.57 ± 0.54	3.63 ± 0.39	3.85 ± 0.42	4.07 ± 0.48	4.18 ± 0.50
3X Females	2.92 ± 0.25	2.92 ± 0.19	2.98 ± 0.23	3.03 ± 0.27	3.08 ± 0.23
5X Males	3.53 ± 0.36	3.68 ± 0.43	3.87 ± 0.49	4.10 ± 0.52	4.25 ± 0.57
5X Females	2.93 ± 0.37	2.90* ± 0.37	2.98 ± 0.40	3.07 ± 0.43	3.05 ± 0.39

*Reported as statistically significant, with a P-value below 0.1 (see p. 43 of MRID 46437615).

Values from Table 3, pp. 44-45, MRID 46437615; individual body weight data on pp. 483-486 of MRID 46437615

F. FOOD CONSUMPTION

From p. 21 of MRID 46437615: "No effect from treatment with R-28153 spot-on formulation was seen in food consumption values. The Placebo Control and treated groups were comparable at all intervals." There was no indication of a significant or biologically relevant drop in food consumption during week 1 in any group; in addition, data for 5X male #136 (4.1 kg on Day 1, dosed with 8 mL formulation, the maximum dose) show no indications of a drop in food consumption.

TABLE 4. Mean Food Consumption (g ± S.D./cat/day) by Group					
Group	Week -1	Week 1	Week 2	Week 3	Week 4
Control Males	122.4 ± 11.0	124.8 ± 28.1	120.8 ± 19.0	129.4 ± 20.6	128.8 ± 32.3
Control Females	103.3 ± 14.3	91.4 ± 8.8	92.7 ± 10.4	93.5 ± 7.1	84.9 ± 12.9
1X Males	116.1 ± 30.9	117.9 ± 26.9	116.3 ± 18.3	118.4 ± 24.4	131.9 ± 39.4
1X Females	101.7 ± 32.6	96.7 ± 13.2	94.5 ± 4.9	104.6 ± 24.0	99.4 ± 25.4
3X Males	132.7 ± 17.1	113.8 ± 15.8	124.7 ± 14.5	136.1 ± 17.5	130.3 ± 18.0
3X Females	100.4 ± 10.7	101.6 ± 22.2	91.6 ± 8.9	98.4 ± 8.6	97.9 ± 9.2
5X Males	124.1 ± 20.5	126.4 ± 27.0	128.8 ± 32.8	138.3 ± 32.2	133.6 ± 25.7
5X Male #136*	151.0	154.2	168.7	170.3	158.3
5X Females	101.4 ± 19.3	90.9 ± 19.5	93.3 ± 15.8	98.3 ± 24.2	100.0 ± 25.8

Group values from Table 5, pp. 64-65, MRID 46437615; individual food consumption data on pp. 509-512 of MRID 46437615; "for logistical reasons, Week 1 food consumption calculated using 6 days."
*Male #136, weighing 4.1 kg on Day 1, was dosed with 8 mL of formulated product, the highest amount of any cat in this study; values are from p. 510.

G. HEMATOLOGY

From p. 21 of MRID 46437615: "No significant test substance effects from treatment with R-28153 spot-on formulation were evident for hematology, coagulation, or clinical chemistry parameters. Several hematology parameters were statistically significant at various intervals. Hemoglobin and hematocrit were increased 24 hours postdose at 3X in gender-pooled samples. These values were comparable to pretest values and not considered an adverse effect of treatment with R-28153 spot-on formulation."

TABLE 5. Means ± S.D. for Hemoglobin (g/dL)				
Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	11.10 ± 1.24	10.35 ± 0.53	10.82 ± 1.17	10.62 ± 0.59
Placebo females	11.47 ± 0.76	11.67 ± 0.64	11.40 ± 0.71	11.13 ± 0.70
1X males	11.23 ± 0.73	11.17 ± 1.40	10.98 ± 0.51	11.07 ± 0.67
1X females	12.10 ± 1.14	11.12 ± 0.49	10.87 ± 0.89	10.83 ± 0.91
3X males	12.20 ± 0.76	**12.05 ± 1.43**	11.72 ± 0.67	12.17 ± 0.85
3X females	12.13 ± 0.56	**12.42 ± 0.88**	11.68 ± 1.13	11.92 ± 1.30
5X males	11.32 ± 0.88	10.60 ± 0.89	10.73 ± 0.96	11.33 ± 1.62
5X females	11.25 ± 1.36	11.12 ± 0.78	10.97 ± 0.77	10.83 ± 1.20

Individual data on p. 794, 795, 807, 808, 820, 821, 833, 834, 846, 847, 859, 860, 872, 873, 885 and 886; Means and Standard Deviations on p. 125 and 126.
P-value for 3X group (combined sexes) at 24 hrs postdose: 0.0273 (from p. 124; statistically significantly different from control values).

TABLE 6. Means ± S.D. for Hematocrit (%)				
Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	37.93 ± 4.35	35.25 ± 1.83	36.20 ± 4.38	35.62 ± 2.09
Placebo females	38.95 ± 2.47	39.63 ± 2.61	38.00 ± 2.61	37.08 ± 2.39
1X males	37.55 ± 2.50	37.32 ± 4.64	36.12 ± 2.03	36.87 ± 2.37
1X females	41.18 ± 4.06	37.93 ± 1.69	36.33 ± 3.06	35.92 ± 3.76
3X males	40.97 ± 1.87	**40.50 ± 4.41**	38.63 ± 1.75	40.77 ± 3.34
3X females	40.73 ± 2.18	**41.52 ± 2.64**	39.60 ± 1.50	39.52 ± 4.23
5X males	38.92 ± 3.07	36.03 ± 2.93	35.80 ± 3.82	38.38 ± 6.07
5X females	38.05 ± 4.88	37.32 ± 2.63	36.18 ± 2.74	36.12 ± 4.19

Individual data on p. 794, 795, 807, 808, 820, 821, 833, 834, 846, 847, 859, 860, 872, 873, 885 and 886; Means and Standard Deviations on p. 133 and 134.
P-value for 3X group (combined sexes) at 24 hrs postdose: 0.0333 (from p. 132; statistically significantly different from control values).

From p. 21: "At 24 hours postdose, platelets were mildly increased in males at 5X and slightly decreased in females at 1X. Platelets were also slightly decreased on Day 22 in males at 3X and females at 1X. Individual platelet values were within normally expected physiological variation."

TABLE 7. Means ± S.D. for Platelets (K/mm^3)				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo males	443.3 ± 149.1	366.7 ± 118.0	316.7 ± 145.5	371.5 ± 125.1
Placebo females	471.2 ± 126.4	491.3 ± 91.1	404.0 ± 137.9	435.7 ± 134.0
1X males	609.8 ± 131.6	530.7 ± 144.3	431.5 ± 152.8	472.5 ± 137.0
1X females	444.8 ± 64.4	**331.7* ± 100.0**	316.5 ± 93.7	**279.2* ± 83.0**
3X males	483.2 ± 150.5	370.8 ± 100.1	271.2 ± 86.2	**273.5* ± 96.0**
3X females	430.7 ± 143.8	434.2 ± 137.9	291.7 ± 195.5	367.8 ± 149.1
5X males	576.7 ± 179.2	**552.0* ± 91.1**	424.7 ± 114.1	500.8 ± 91.0
5X females	438.2 ± 82.3	419.0 ± 110.5	326.0 ± 150.1	403.3 ± 91.4

Individual data on p. 794, 795, 807, 808, 820, 821, 833, 834, 846, 847, 859, 860, 872, 873, 885 and 886; Means and Standard Deviations on p. 162 and 163.
*P-value for 5X males at 24 hrs postdose: 0.0389; for 3X males on Day 22: 0.0365; for 1X females at 24 hrs postdose: 0.0096; for 1X females on Day 22: 0.0126 (from p. 161)

From http://www.ahc.umn.edu/rar/RefValues.html the normal reference range for platelet counts for the cat is 160-660 K/mm^3. The range of values seen in this study was 83 (observed in 3X female #121 on Day 8) to 836 K/mm^3 (observed in a 5X male at pretest; the highest value observed after dosing was 709 K/mm^3). 3X female #121 had a platelet count of 477 K/mm^3 predose, 325 K/mm^3 at 24 hours postdose, 83 K/mm^3 on Day 8, and 219 K/mm^3 on Day 22. While 3X female #138 had a platelet count of 122 K/mm^3 on Day 8 this cat also had a low platelet count (154 K/mm^3) at predose.

Activated Partial Thromboplastin Time (APTT) was somewhat increased in all groups (including Placebo Controls) at 24 hours and 8 days.

TABLE 8. Means ± S.D. for APTT (sec)				
Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	17.17 ± 4.85	22.87 ± 3.56	24.38 ± 10.18	15.32 ± 2.53
Placebo females	21.48 ± 6.67	26.27 ± 5.55	21.60 ± 5.94	18.87 ± 1.64
Placebo combined	19.33 ± 6.00	24.57 ± 4.79	22.99 ± 8.08	17.09 ± 2.75
1X males	17.82 ± 1.74	24.92 ± 5.41	27.27 ± 6.97	18.42 ± 3.22
1X females	18.77 ± 3.94	23.52 ± 5.55	19.35 ± 5.45	16.55 ± 2.75
1X combined	18.29 ± 2.95	24.22 ± 5.28	23.31 ± 7.26	17.48 ± 3.02
3X males	20.53 ± 8.03	27.87 ± 7.86	21.98 ± 5.74	19.07 ± 2.74
3X females	15.75 ± 3.50	21.40 ± 5.70	25.27 ± 7.92	19.02 ± 4.13
3X combined	18.14 ± 6.41	24.63 ± 7.37	23.63 ± 6.82	19.04 ± 3.34
5X males	16.20 ± 3.27	24.38 ± 11.12	19.68 ± 3.99	22.57 ± 6.72
5X females	22.22 ± 9.30	24.48 ± 13.58	24.88 ± 5.25	18.85 ± 7.49
5X combined	19.21 ± 7.35	24.43 ± 11.83	22.28 ± 5.21	20.71 ± 7.05

Individual data on p. 798, 799, 811, 812, 824, 825, 837, 838, 850, 851, 863, 864, 876, 877, 889 and 890; Means and Standard Deviations on p. 192, 193 and 197.

There was no statistical significance to the increase in APTT times at 24 hours and 8 Days, as the P=0.1251 for the pretreatment covariate for 24 hours and P=0.2148 for the pretreatment covariate for Day 8.

From p. 22 of MRID46437615: "Punctate and total reticulocytes were increased in males at 5X on Day 22 but with no decrease in red blood cell parameters, these were of no toxicological significance."

"Neutrophils were increased on Day 22 for gender-pooled samples at 3X, but individual values were within expected ranges. Eosinophils were increased in males at 1X, 3X, and 5X to the magnitude of 2.45, 1.58 and 2.97 times, respectively, and decreased in females at 1X on Day 8. The increase in eosinophils in males did not demonstrate a clear dose-dependant response, yet the magnitude of the increase at each dose level, considered along with the decrease in eosinophils in females at 1X, could indicate a treatment effect in males only to treatment with R-28153 spot-on formulation."

TABLE 9. Means ± S.D. for Neutrophils (K/µL)				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo males	7.095 ± 1.853	5.442 ± 2.339	8.430 ± 5.871	6.448 ± 2.951
Placebo females	7.348 ± 3.003	8.592 ± 3.685	7.503 ± 1.813	4.808 ± 1.143
Placebo combined	7.222 ± 2.383	7.017 ± 3.372	7.967 ± 4.171	5.628 ± 2.299
1X males	7.623 ± 2.684	7.763 ± 3.553	8.333 ± 3.013	6.745 ± 1.622
1X females	7.042 ± 2.616	8.333 ± 2.186	8.002 ± 3.922	6.370 ± 4.271
1X combined	7.333 ± 2.545	8.048 ± 2.828	8.168 ± 3.339	6.558 ± 3.087
3X males	8.897 ± 3.539	6.673 ± 2.148	9.395 ± 2.964	8.117 ± 2.594
3X females	7.442 ± 3.492	5.898 ± 1.561	7.557 ± 1.795	8.355 ± 2.764
3X combined	8.169 ± 3.437	6.286 ± 1.835	8.476 ± 2.526	8.236 ± 2.559
5X males	8.438 ± 4.003	8.700 ± 4.887	9.777 ± 4.198	8.890 ± 2.928
5X females	6.162 ± 1.921	5.378 ± 1.093	5.908 ± 2.703	5.280 ± 3.138
5X combined	7.300 ± 3.221	7.039 ± 3.796	7.843 ± 3.926	7.085 ± 3.454

Individual data on p. 800, 801, 813, 814, 826, 827, 839, 840, 852, 853, 865, 866, 878, 879, 891 and 892; Means and Standard Deviations on p. 207, 208 and 212.

Examination of individual neutrophil data for males (pp. 826-827) indicates the high values on Day 8 involved high counts from 1-3 males/group (placebo controls: #101: 12.34; #119: 10.51; #143: 16.70; 1X: #142: 13.35; 3X: #112: 10.57; #134: 13.91; 5X: #117: 15.94; #125: 10.57; #136: 12.34).

TABLE 10. Means ± S.D. for Eosinophils (K/µL))				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo males	0.963 ± 0.608	1.228 ± 0.942	0.800 ± 0.456	0.770 ± 0.415
Placebo females	1.015 ± 0.391	1.378 ± 0.837	1.925 ± 1.083	0.913 ± 0.359
Placebo combined	0.989 ± 0.488	1.303 ± 0.853	1.363 ± 0.986	0.842 ± 0.377
1X males	1.177 ± 0.385	2.047 ± 1.388	**1.962 ± 0.961**	1.058 ± 0.461
1X females	1.043 ± 0.281	1.705 ± 0.804	1.127 ± 0.578	1.365 ± 0.672
1X combined	1.110 ± 0.329	1.876 ± 1.096	1.544 ± 0.873	1.212 ± 0.572
3X males	0.882 ± 0.547	1.025 ± 0.553	**1.267 ± 0.445**	1.183 ± 0.942
3X females	1.157 ± 0.292	1.853 ± 0.578	1.598 ± 0.573	1.083 ± 0.312
3X combined	1.019 ± 0.442	1.439 ± 0.691	1.433 ± 0.519	1.133 ± 0.671
5X males	0.738 ± 0.377	1.103 ± 0.584	**2.375 ± 3.270**	0.820 ± 0.376
5X females	1.258 ± 0.661	2.035 ± 1.620	1.343 ± 0.632	0.787 ± 0.432
5X combined	0.998 ± 0.580	1.569 ± 1.259	1.859 ± 2.309	0.803 ± 0.387

Individual data on p. 800, 801, 813, 814, 826, 827, 839, 840, 852, 853, 865, 866, 878, 879, 891 and 892; Means and Standard Deviations on p. 229, 230 and 234. From information on p. 227 at 24 hours there was a pretreatment covariate effect with P=0.0016; on Day 8 P=0.0130, and on Day 22 P=0.0044 On Day 8 the 1X male value was significantly different from the control value at P=0.0145; for the 3X male value P=0.0603, and for the 5X male value P=0.0089.

The relatively high mean value for eosinophils in 5X males on Day 8 was largely due to a single high value in one cat (#141: value 9.02 x 10^3/µL); the mean value for the remaining 5 males in this group was 1.046 (range: 0.65-1.53) x 10^3/µL.

H. CLINICAL CHEMISTRY

From p. 22: "For clinical chemistry parameters, total bilirubin was decreased in gender-pooled samples at 1X on Day 8 and globulin at 1X and 5X on Day 22. Creatinine was mildly increased in females at 3X and 5X on Day 8. The direction and minimal magnitude of these changes are not toxicologically significant."

From information on pages 332-333 the values for total bilirubin obtained in the course of this study generally fell within a tight range (0.1 to 0.3 mg/dL). Group means ranged from 0.18 to 0.23 mg/dL, and there was a frequent group/sex occurrence of a mean of 0.20 with a SD of 0.00 (all 6 males or females in a group at a timepoint had the same value of 0.20). There is no indication then of an effect involving this parameter associated with R-28153 spot-on treatment.

The statistically significant decreases in globulin on Day 22 in gender-pooled samples at the 1X and 5X dose levels were not biologically relevant (from p. 405: mean values, in g/dL: Placebo Control: 3.14; 1X: 3.06; 3X: 3.11; 5X: 3.02).

From information on p. 378 the statistical significance for Creatinine on Day 8 involves a relatively low mean value (0.90 mg/dL) for the female placebo control group. The Day 8 mean value for 3X females was 0.98 mg/dL (individual range: 0.8 to 1.1 mg/dL) and for 5X females was 0.95 mg/dL (individual range: 0.7 to 1.2 mg/dL). The pretest female placebo control value was 0.97 mg/dL; at 24 hours it was 0.95 mg/dL and on Day 22 it was 1.07 mg/dL. There is no biological relevance associated with these occurrences of statistical significance (female 3X on Day 8 relative to control value: P=0.0130; female 5X on Day 8 relative to control value: P=0.0479).

I. NECROPSY FINDINGS

As there were no mortalities, there were no necropsy findings.

IV. DISCUSSION

This is the first application for registration that the Agency has received for an R-28153 spot-on formulation for cats.

According to proposed label directions the product would be applied as a spot-on with the following dosage rates: cats $\leq$ 4 kg (up to 9 lbs): 0.8 mL; > 4 kg (> 9 lbs): 1.6 mL.

In this companion animal safety study (MRID 46437615), 4 groups, each containing 12 (6/sex) young (173-245 days old) adult cats (source: Liberty Research Inc., Waverly, NY; males: 2.2 to 4.5 kg; females: 1.8-3.5 kg) were treated at 0X (4.0 or 8.0 mL placebo), 1X (0.8 or 1.6 mL spot-on formulation), 3X (2.4 or 4.8 mL spot-on formulation) and 5X (4.0 mL or 8.0 spot-on formulation; lower doses in each group were for cats weighing less than 4 kg, while higher doses were for cats weighing more than 4 kg; one male and no females in each group weighed more than 4 kg). Application to each cat was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the syringe was dragged back slowly distally.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Cats were individually weighed on Days -15, -8, -1, and then postdose on Days 7, 14, 21 and 28. Food consumption is reported (g/cat/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (about 24 hours postdose), 8 and 22.

All cats survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of cats (including some in the placebo group) from 15 minutes postdose and continuing through 2 hours postdose with the following incidences: placebo control: 2/6M, 3/6F; 1X: 1/6M, 2/6F; 3X: 0/6M, 2/6F; 5X: 2/6M, 1/6F. Salivation was also seen in a 1X male at the physical examination on Day 1 (day of dosing) and in a 5X female on Day 2. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

One 3X female (#121) had a drop in platelet count on Day 8 with a recovery on Day 22 (Pretest: 477 K/mm^3; 24 hrs: 325 K/mm^3; Day 8: 83 K/mm^3; Day 22: 219 K/mm^3). However, this was an isolated case, as a similar effect was not observed in any of the other cats.

Activated Partial Thromboplastin Time (APTT) was somewhat increased in all groups (including Placebo Controls) at 24 hrs and 8 Days. For combined sexes the following mean values were obtained at 24 hours postdose (pretest values = 1.00): Placebo Control: 1.27; 1X: 1.32; 3X: 1.36; and 5X: 1.27. Corresponding values on Day 8 were: Placebo Control: 1.19; 1X: 1.27; 3X: 1.30; 5X: 1.16. Day 22 and predose values were essentially the same. In the absence of any indication of a dose-related trend, it is doubtful that this finding is associated with exposure to either the active or inerts in this formulation. In addition, the degree of elevation is biologically non-significant.

Mean eosinophil counts were significantly increased in males relative to their controls on Day 8, values (with controls = 1.00) were: 1X: 2.45; 3X: 1.58; 5X: 2.97. However, this was not concurrently observed in females, as their corresponding group values relative to the control were: 1X: 0.59; 3X: 0.83; 5X: 0.70. Also, the relatively high mean value for 5X males on Day 8 was largely due to a single high value in one cat (#141: value 9.02 x 10^3/µL), and the mean value for the remaining 5 males in this group was 1.05 (range: 0.65-1.53) x 10^3/µL (1.05 x 10^3/µL = 1.31X the concurrent control value). The value for cat #141 had dropped to a more normal 1.19 x 10^3/µL by Day 22. This temporary eosinophilia was probably spontaneous in nature (it may have involved an immune response to intestinal parasites).

Sporadic statistically significant changes involving clinical chemistry parameters (total bilirubin, globulin, creatinine) in gender-pooled samples or in one sex were not biologically relevant, as they were minimal and individual values fell within normal ranges.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for adult cats, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation in adult cats. While salivation was noted (mostly in the 2-hour period following application) this was probably associated with ingestion from grooming and/or the odor and/or taste of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Exposure or ingestion may result in temporary salivation; this a response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

EPA Primary Reviewer: Byron T. Backus, Ph.D. **Signature:** _____
Technical Review Branch, Registration Division (7505C) **Date** _____
EPA Secondary Reviewer: John Redden, M.S. **Signature:** _____
Technical Review Branch, Registration Division (7505C) **Date** _____

DATA EVALUATION RECORD

STUDY TYPE: **Companion Animal Safety - Eight Week Old Kittens (OPPTS 870.7200)**

PC CODE: 281250 (Metaflumizone; R-28153)

DP BARCODE: D314413 **RISK MANAGER: (EPA): 07** **DECISION NO.: 354816**

PRODUCT AND TEST MATERIAL: 20% w/v R-28153 spot-on formulation, Lot No. 0381704, a pale yellow liquid with a specific gravity of 1.085 g/mL containing (from p. 424 of MRID 464376-16) 20.3% R-28153 (Metaflumizone).

CITATION: Lindahl, R.G. (2004) Safety Evaluation Study of a Topically Applied Spot-On Formulation of R-28153 in Eight Week Old Kittens. Study No. 817-010; Sponsor Study No. 0817-F-US-03-03. Unpublished study prepared by MPI Research, Inc. 54943 North Main St. Mattawan, MI 49071-9399. Study Completion Date: 11 May 2004. MRID 46437616.

SPONSOR: Fort Dodge Animal Health, PO Box 5366, Princeton, NJ 08543-5366.

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46437616), 4 groups, each containing 12 (6/sex) 53-57 day-old kittens (source: Liberty Research Inc., Waverly, NY; weights on Day -1: males: 0.568 to 0.866 kg; females: 0.566 to 0.855 kg) were treated at 0X (4.0 mL placebo), 1X (0.8 mL spot-on formulation), 3X (2.4 mL spot-on formulation) and 5X (4.0 mL spot-on formulation). Application to each kitten was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the dispensing syringe was dragged back slowly distally.

According to proposed label directions the product would be applied as a spot-on with a dosage rate of 0.8 mL for cats and kittens $\leq$ 4 kg and 1.6 mL for cats >4 kg.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Kittens were individually weighed on Days -14, -12, -9, -7, -5, -2, -1, and then postdose on Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 and 29. Food consumption is reported (g/kitten/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (24 hours postdose), 8 and 22. If redraws were necessary these were collected approximately 48 hours after the initial draws.

All kittens survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of kittens (including some in the placebo group) at 1 hour postdose with the following incidences: placebo control: 3/6M, 2/6F; 1X: 0/6M, 0/6F; 3X: 1/6M, 1/6F; 5X: 1/6M, 3/6F. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

Sporadic statistically significant differences involving hematology and clinical chemistry parameters (leukocyte counts, MCHC, prothrombin time, alkaline phosphatase activity, potassium and chloride) in gender-pooled samples or in one sex were not biologically relevant, as they were not exposure/dose-related, were generally minimal, and individual values tended to fall within normal ranges. Similar changes in the same parameters were not observed in the adult cat study (MRID 46437615) with this formulation.

As no kittens weighing more than 4 kg were tested in this study, labeling should indicate that no more than 0.8 mL should be applied to kittens of 6 months of age.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for 8-week-old kittens, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation at an application of rate of 0.8 mL/dose. While salivation was noted (in the 2-hour period following application) this may have been associated with ingestion from grooming and/or the odor and/or taste [possibly from dermal absorption] of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Ingestion or exposure may result in a brief period of salivation; this response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

COMPLIANCE: Signed and dated Quality Assurance (p. 8), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: 20% w/v R-28153 Spot-on, with a label declaration of 18.53% Metaflumizone (also known as BAS 320 I). According to a certificate of analysis on p. 424 of MRID 46437616 the test formulation contained 20.3% (average of 6 vials) w/w R-28153 and had a specific gravity of 1.085 g/mL.
   Description: Clear yellow liquid
   Lot No.: 0381704 (manufactured November 5, 2003)
   Storage: Room Temperature, with protection from light

   Placebo: 0% w/v R-28153 Placebo. This formulation assayed 0.00% w/v R-28153. The specific gravity is reported (p. 423 of MRID 46437616) as 1.031.
   Description: Clear light yellow liquid
   Lot No.: 0381703 (manufactured November 3, 2003)
   Storage: Room Temperature, with protection from light

2. Administration: Topical (spot-on) on Day 1

3. Test animals
   Species: Cat
   Breed: Not indicated
   Ages and weights at study initiation (Day 1, day of dosing): Males: 53 days to 58 days (see p. 431-432); 0.568 to 0.866 kg (see p. 426-427); Females: 53 days to 57 days (see p. 433-434); 0.566 to 0.855 kg (see p. 428-429). Kittens were born between October 21, 2003 and October 25, 2003.
   Source: Liberty Research Inc., Waverly, New York
   Housing: individually housed from Day -5
   Diet: Hills Prescription Diet Feline Canned Food, *ad libitum*, except during fasting periods.
   Water: Tap water, *ad libitum*
   Environmental conditions:
      Temperature: 74° -84°C
      Humidity: 30 - 70%
      Air changes: not stated
      Photoperiod: approximately 12 hours light/day
   Acclimation period: 2 weeks

II. STUDY DESIGN

A. IN LIFE DATES

From the report: Application (see p. 10): December 17, 2003; experimental termination date: January 14, 2004.

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 12 (6 male, 6 female) kittens per dosage group. Kittens in the placebo control group were treated at with 4.0 mL placebo formulation, at 1X with 0.8 spot-on formulation, at 3X with 2.4 mL spot-on formulation and at 5X with 4.0 mL spot-on formulation. Application to each kitten was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the syringe was dragged back slowly distally.

From p. 14 of MRID 46437616: "The test and placebo control substances were administered once on Day 1 (December 17, 2003) by topical application. The animal was held in a position such that the surface to be treated was easily accessible. A section of hair between the shoulder blades on the dorsal midline extending cranially and caudally was separated. A Becton Dickinson disposable syringe containing the appropriate amount of test substance was placed through the hair to the skin and the test or control substance was applied by dragging the syringe back slowly distally along the dorsal midline while applying the dose. Due to varying dose volumes, a 5 mL syringe was used for whole mL volumes and a 1 mL syringe was used for volumes less than 1 mL. Care was taken when applying the test substance to reduce the chance of run-off, and no run-off was observed. Separate syringes were used to apply each test or control substance, and gloves were changed between test and control substance application..."

TABLE 1. Study design							
Group & Weight Range (kg)		Number of kittens		Cumulative Dose/cat			
		Male	Female	Total/ Kitten	Mean Kitten Wt ± S.D. (g)[a]	Mean Dose mg/kg	Mean Dosage Metaflumizone (mg/kg)[f]
Placebo Control	<4.0	6	6	4.0 mL[b] 4124 mg[c]	714 ± 71 (M) 642 ± 37 (F) 678 ± 66 (C)	5776(M)[b] 6424(F)[b] 6083(C)[b]	0(M) 0(F) 0(C)
1X	<4.0	6	6	0.8 mL[d] 868 mg[e]	706 ± 101 (M) 671 ± 94 (F) 688 ± 95 (C)	1229[e](M) 1294[e](F) 1262[e](C)	249.5 (M) 262.7 (F) 256.2 (C)
3X	<4.0	6	6	2.4 mL[d] 2604 mg[e]	693 ± 91 (M) 681 ± 109 (F) 687 ± 96 (C)	3758[e](M) 3824[e](F) 3790[e](C)	762.9 (M) 776.3 (F) 769.4 (C)
5X	<4.0	6	6	4.0 mL[d] 4340 mg[e]	686 ± 86 (M) 669 ± 69 (F) 677 ± 75 (C)	6327[e](M) 6487[e](F) 6411[e](C)	1284.4 (M) 1316.9 (F) 1301.4 (C)

[a] Calculated from information on p. 426-429 of MRID 46437616.
[b] Placebo
[c] Based on a specific gravity for the placebo of 1.031 g/mL (see p. 423 of MRID 46437616).
[d] Test material (with actives); amount delivered.
[e] Based on a specific gravity for the test material of 1.085 g/mL (see p. 424 of MRID 46437616).
[f] Based on 20.3% active ingredient (see p. 424 of MRID 46437616).

C. DOSE SELECTION RATIONALE

From p. 13 of MRID 46437616: "The target minimum dose was 160 mg/kg for kittens less than or equal to 4 kg. Each mL contains 200 mg of R-28153. The intended product package is for weight bands (≤ 4 kg and >4 kg), therefore dosing was applied at the same volume for each individual animal within the specified weight range. Evaluation of the safety of the test substance at up to five times the proposed *ad usum* rate in kittens provided an appropriate safety margin for the planned therapeutic dose."

According to the proposed label this product will be packaged in 6-packs of monthly unidose applicators with the following single dosages: 0.8 mL (for cats and kittens up to 9 lb) and 1.6 mL (for cats weighing more than 9 lb). Application directions include a specification to apply the entire content of an applicator tube to the cat's skin and not to apply to the surface of the cat's fur.

D. EXPERIMENTAL DESIGN

From p. 14 of MRID 46437616: "On Day 1, detailed clinical observations were conducted predose, immediately postdose, and at 1, 2, and 3 hours postdose. Clinical observations were also conducted twice daily (except once daily on Days -13, -1, 2, 8, and 22 due to physical and neurological examinations) during the course of the study..."

Kittens were individually weighed on Days -14, -12, -9, -7, -5, -2, -1, and then postdose on Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 and 29. Food consumption is reported (g/kitten/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (24 hours postdose), 8 and 22. If redraws were necessary these were collected approximately 48 hours after the initial draws.

Individual food consumption was measured daily and reported weekly (beginning the last four days of the pretest period and continuing weekly through study termination).

E. PATHOLOGICAL PARAMETERS

Blood samples were collected from each cat once pretest (Week -1), and on Days 2 (approximately 24 hours postdose), 8 and 22 by jugular venipuncture following an

overnight fast. Several redraws were necessary and were made approximately 48 hours after the initial draws. 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	Punctate reticulocytes
	Blood clotting measurements	X	Aggregate reticulocytes
	(Thromboplastin time)	X	Percent reticulocytes
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		

*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*	X	Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total bilirubin (T Bil)*
	ENZYMES		Direct bilirubin (D Bil)*
X	Alkaline phosphatase(ALPor ALK)*	X	Total serum protein (TP)*
	Cholinesterase(ChE)		Triglycerides
X	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)	X	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)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

A statistical summary report is found in Appendix M, pages 1128 to 1133 of MRID 46437616. From p. 16 of MRID 4643616: "Each of the four treatment groups contained one animal from each of six blocks for each sex. Data were summarized, in tabular form, for each group by mean, standard deviation, number of animals examined, minimal value, and maximum value."

For body weight: "Statistical analysis was performed on body weight change at Days 6, 13, 20, and 27 using the PROC MIXED procedure in SAS with treatment, sex and treatment by sex as fixed effects. First the treatment by sex interaction was tested at the 5% level of significance. If the treatment by sex interaction was found significant, then the treated groups' LSMeans were compared to the control group LSMean for each sex by the 2-sided Student's t-test at the 10% level for that parameter. If the treatment by sex interaction was found not to be significant and treatment effect was found to be significant at the 10% level, treated groups' LSMeans were compared with LSMean of the control group by the 2-sided Student's t-test at the 10% level. If treatment by sex interaction, and treatment effect were found not significant for a parameter, no further analysis for that parameter was done at this step and treatments were considered to have no effect on body weight change from baseline."

For body weight and food consumption: "A repeated measure analysis was performed on body weight and food consumption parameters using the PROC MIXED procedure in SAS. The model contained pretreatment measurements at Week -1 for food consumption and Day -1 for body weight as the corresponding covariate, and treatment, sex, treatment by sex, week, sex by week, treatment by sex by week, and treatment by

week as the fixed effects and interactions with week as the repeated fix effect... If treatment by sex by week interaction was found significant at the 5% level for a parameter, no further analysis was done for that parameter... If treatment by sex by week interaction was found not significant for a parameter, then treatment by sex interaction was tested at the 5% level of significance and treatment by week and sex by week interactions were tested at the 10% levels for that parameter. If treatment by sex interaction was found significant for the parameter, then the treated groups' LSMeans were compared to the control group LSMean for each sex by the 2-sided Student's t-test at the 10% level..."

From p. 18: "For all the quantitative hematology, coagulation and clinical chemistry parameters, pretreatment measurements were considered covariant in the analysis. For count data such as leukocyte count, etc., log-transformation was used. The individual parameters were analyzed by time (i.e. 24 hours postdose, and Days 8 and 22) for hematology, coagulation and clinical chemistry parameters by the PROC MIXED procedure with pretreatment measurements as corresponding covariates, and treatment, sex and treatment by sex as fixed main effects and interaction..."

G. DISPOSITION OF ANIMALS

From p. 15 of MRID 46437616: "The animals were euthanized via intravenous injection of sodium pentobarbital on January 14, 2004..." 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. 8], [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. Kittens in the placebo control group received 4.0 mL of the placebo formulation (the product less 20.3% R-28153). As a result, they received an approximately 5.96x dose of the "other ingredients" that the 1X group received. Kittens in the 1X group received 0.8 mL formulated product; those in the 3X group received 2.4 mL formulated product, while those in the 5X group received 4.0 mL formulated product.

B. MORTALITY

There was no mortality, with all kittens surviving the 28-day observation period.

C. CLINICAL SIGNS

It is stated (p. 20 of MRID 46437616) that: "Salivation was noted for three Placebo Control males, one male at 3X, and one male at 5X at the 1 hour postdose interval. Similarly, salivation was noted for two Placebo Control females, one female at 3X, and three females at 5X at the 1 hour postdose interval. This reaction is most likely a transitory effect of treatment, but as the observation was also noted in the Placebo Controls, it is not considered an effect of R-28153 spot-on formulation."

TABLE 2. Incidences of Salivation Observed in Kittens Treated with R-28153 Spot-on In the Period Immediately Following Treatment[a]				
Observation	**Placebo (Vehicle) Control**	**1X**	**3X**	**5X**
Salivation at immediate postdose	0/6M; 0/6F	0/6M; 0/6F	0/6M; 0/6F	0/6M; 0/6F
Salivation at 1 hr postdose	3[b]/6M; 2[b]/6F	0/6M; 0/6F	1[b]/6M; 1[b]/6F	1[b]/6M; 3[b]/6F
Salivation at 2 hrs postdose	0/6M; 0/6F	0/6M, 0/6F	0/6M; 0/6F	0/6M; 0/6F
Salivation at 3 hrs postdose	0/6M; 0/6F	0/6M, 0/6F	0/6M; 0/6F	0/6M; 0/6F
Salivation at 15 minutes or 1 hr or 2 hrs postdose	3/6M; 2/6F	0/6M; 0/6F	1/6M; 1/6F	1/6M; 3/6F

[a]Data taken from Appendix D, Section C, p. 448-467 of MRID 46437616.
[b]Males showing salivation at 1 hr were: Controls: 119, 125, 136; 1X: none; 3X: 133; 5X: 127; females showing salivation at 1 hr were: Controls: 106, 146; 1X: none; 3X: 115; 5X: 116, 131, 145.

One control female (#124) vocalized postdose (see p. 460 of MRID 46437616).

From p. 437 of MRID 46437616: "One 5X male kitten (animal number 120) had soft feces at the A.M. and P.M. observations on Day 5 only... One female kitten (animal number 123) at 3X had material around the nose, audible breathing, and coughing, at both observations on Day 10 only."

The statement is made (p. 437 of MRID 46437616) that: "Except for the salivation noted at 1 hour postdose, the clinical observations noted were considered minimal and may occasionally be encountered in kittens of this age and species/breed. The salivation noted in 11 of the 48 kittens at 1 hour postdose only may indicate a transitory reaction to the treatments."

From p. 21: "The few physical signs noted (clear ocular discharge, soft feces, coughing, lacerations/abrasions) were seen across all groups, including the Placebo Control, and are not uncommon in kittens of this age."

D. NEUROLOGICAL EXAMINATIONS

From p. 21: "No significant neurological findings were noted. Neurological examinations were within normal parameters at all examination intervals." This statement is consistent with the individual neurological examination findings reported in Appendix H Section C [pp. 537-632 of MRID 46437615].

E. BODY WEIGHT AND WEIGHT GAIN

From p. 20 of MRID 46437616: "Treatment with R-28153 spot-on formulation had no effect on body weight. A significant sex by period interaction was noted and subsequent analysis indicated a significant increase in body weight for female kittens at 5X on Days 13 and 20. Body weight for the males at 1X, 3X, and 5X was comparable to the Placebo Controls. Body weight change was also unaffected and as a result, the increase noted in the females was not considered an effect of treatment with R-28153 spot-on formulation."

TABLE 3. Mean Body Weights for Kittens by Group					
Group	kg ± S.D.				
	Day -1	Day 6	Day 13	Day 20	Day 27
Control Males	0.714 ± 0.072	0.849 ± 0.048	0.986 ± 0.055	1.155 ± 0.068	1.281 ± 0.055
Control Females	0.642 ± 0.037	0.754 ± 0.045	0.832 ± 0.057	0.974 ± 0.102	1.099 ± 0.100
1X Males	0.706 ± 0.101	0.827 ± 0.133	0.927 ± 0.149	1.088 ± 0.173	1.234 ± 0.160
1X Females	0.671 ± 0.094	0.792 ± 0.111	0.898 ± 0.100	1.039 ± 0.090	1.159 ± 0.103
3X Males	0.693 ± 0.091	0.825 ± 0.121	0.956 ± 0.105	1.114 ± 0.123	1.252 ± 0.111
3X Females	0.681 ± 0.109	0.792 ± 0.130	0.900 ± 0.139	1.056 ± 0.176	1.179 ± 0.175
5X Males	0.686 ± 0.086	0.821 ± 0.109	0.960 ± 0.119	1.147 ± 0.164	1.275 ± 0.117
5X Females	0.669 ± 0.069	0.814 ± 0.067	0.932* ± 0.058	1.085* ± 0.068	1.199 ± 0.064

Values from Table 3, pp. 44-45 of MRID 46437616; individual body weight data on pp. 477-484 of MRID 46437616.

*Reported as statistically significant, with a P-value below 0.1 (see p. 43 of MRID 46437616).

F. FOOD CONSUMPTION

From p. 21 of MRID 46437616: "Food consumption in both males and females was comparable to the Placebo Control for all of the treated groups. No effect from treatment with R-28153 spot-on formulation was evident."

TABLE 4. Mean Food Consumption (g ± S.D./kitten/day) by Group					
Group	Week -1	Week 1	Week 2	Week 3	Week 4
Control Males	106.7 ± 9.7	123.2 ± 9.1	130.5 ± 12.2	155.2 ± 15.5	159.4 ± 10.6
Control Females	92.8 ± 9.0	116.0 ± 23.3	111.1 ± 26.4	141.8 ± 39.5	144.3 ± 20.0
1X Males	100.7 ± 19.0	113.9 ± 20.3	116.7 ± 22.5	152.4 ± 24.8	153.5 ± 11.8
1X Females	102.8 ± 17.4	111.5 ± 12.9	116.4 ± 14.6	135.8 ± 14.3	144.4 ± 11.9
3X Males	103.8 ± 24.6	116.6 ± 22.9	125.8 ± 13.3	150.5 ± 15.9	158.6 ± 9.0
3X Females	97.8 ± 18.1	113.5 ± 27.0	115.4 ± 25.3	149.2 ± 34.0	149.7 ± 26.2
5X Males	95.8 ± 20.3	118.3 ± 19.5	128.7 ± 18.1	164.1 ± 23.2	161.0 ± 12.0
5X Females	108.5 ± 10.9	122.0 ± 10.4	129.7 ± 9.3	153.1 ± 8.7	156.2 ± 6.5

Group values from Table 5, pp. 64-65, MRID 46437616; individual weekly food consumption data on pp. 511-514 of MRID 46437616: "For logistical reasons, Week 1 food consumption calcuated using 6 days." Week -1 food consumption was calculated using 4 days.

G. HEMATOLOGY

From p. 21 of MRID 46437616: "Hematology and coagulation parameters were not adversely affected from treatment with R-28153 spot-on formulation. Leukocytes were increased in gender-pooled samples at 1X and 3X on Day 8. These increases were mild, were reflected in variably increased neutrophils or lymphocytes (but not to a statistically significant degree), and did not exhibit a dose-dependent pattern. They are not considered to be test-article related. Increased MCHC at 24 hours postdose and at Day 8 [in the pooled 1X group] was not considered physiologically meaningful due to the low magnitude of the increase. Prothrombin time was decreased in 5X females at 24 hours postdose but the magnitude and direction of this result was not sufficient to be considered physiologically meaningful. All of these effects were not considered to be clinically detrimental."

TABLE 5. Means ± S.D. for Leukocytes (K/mm^{-3})				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo male	13.65 ± 4.62	13.83 ± 3.21	14.95 ± 4.28	16.78 ± 6.31
Placebo females	16.22 ± 4.65	16.68 ± 5.06	19.43 ± 6.10	24.13 ± 7.24
Placebo pooled	14.93 ± 4.62	15.26 ± 4.30	17.19 ± 5.54	20.46 ± 7.53
1X males	14.02 ± 3.65	17.45 ± 3.96	22.02 ± 3.52	19.85 ± 3.84
1X females	18.23 ± 5.77	15.08 ± 5.09	19.23 ± 5.65	22.42 ± 10.80
1X pooled	16.13 ± 5.11	**16.27 ± 4.52**	20.63 ± 4.71	21.13 ± 7.85
3X males	11.82 ± 2.56	14.77 ± 4.79	20.85 ± 3.50	21.27 ± 4.44
3X females	16.32 ± 4.57	17.78 ± 6.36	21.05 ± 3.59	20.52 ± 6.39
3X pooled	14.07 ± 4.24	**16.28 ± 5.59**	20.95 ± 3.38	20.89 ± 5.26
5X males	10.90 ± 3.95	15.42 ± 6.01	16.28 ± 5.67	14.95 ± 4.57
5X females	11.20 ± 3.04	13.60 ± 4.94	14.85 ± 2.22	14.97 ± 3.47
5X pooled	11.05 ± 3.36	14.51 ± 5.33	15.57 ± 4.17	14.96 ± 3.87

Individual data on p. 792, 793, 805, 806, 818, 819, 831, 832, 844, 845, 857, 858, 870, 871, 883 and 884. Means and Standard Deviations on p. 111, 112 and 116.

Day 8: P-value for 1X group (combined sexes): 0.0544; P-value for 3X group (combined sexes): 0.0064 (from p. 110; reported as statistically significantly different from concurrent control values).

TABLE 6. Means ± S.D. for MCHC mg/dL)				
Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	29.43 ± 1.39	28.75 ± 0.90	28.32 ± 0.95	28.87 ± 0.81
Placebo females	29.32 ± 1.04	28.13 ± 0.68	27.80 ± 0.70	28.20 ± 0.79
Placebo pooled	29.38 ± 1.17	28.44 ± 0.82	28.06 ± 0.84	28.53 ± 0.84
1X males	29.33 ± 8.44	30.13 ± 1.61	29.27 ± 0.62	28.92 ± 0.59
1X females	29.80 ± 1.17	29.93 ± 1.48	28.42 ± 0.59	28.90 ± 0.85
1X pooled	29.57 ± 5.75	**30.03 ± 1.48**	**28.84 ± 0.72**	28.91 ± 0.70
3X males	31.20 ± 2.07	29.30 ± 1.98	28.82 ± 1.06	28.55 ± 1.02
3X females	28.87 ± 1.07	29.00 ± 1.20	27.90 ± 0.72	28.25 ± 1.37
3X females	30.03 ± 1.99	29.15 ± 1.57	28.36 ± 0.99	28.40 ± 1.16
5X males	30.10 ± 1.73	29.42 ± 1.11	28.60 ± 0.91	28.58 ± 1.06
5X females	30.37 ± 2.06	29.17 ± 0.91	27.68 ± 0.48	28.32 ± 0.55
5X females	30.23 ± 1.82	29.29 ± 0.98	28.14 ± 0.84	28.45 ±0.82

Individual data on p. 792, 793, 805, 806, 818, 819, 831, 832, 844, 845, 857, 858, 870, 871, 883 and 884. Means and Standard Deviations on p. 154, 155 and 159.
P-value for 1X group (combined sexes) at 24 hrs postdose: 0.0034; Day 8: 0.0132 (from p. 153; statistically significantly different from concurrent control values).

From p. 21: "At 24 hours postdose, platelets were mildly increased in males at 5X and slightly decreased in females at 1X. Platelets were also slightly decreased on Day 22 in males at 3X and females at 1X. Individual platelet values were within normally expected physiological variation."

TABLE 7. Means ± S.D. for Prothrombin Time (sec)				
Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	9.02 ± 0.95	9.15 ± 0.72	9.13 ± 0.51	8.00 ± 1.11
Placebo females	9.57 ± 1.40	10.37 ± 1.39	9.22 ± 1.59	7.90 ± 1.25
Placebo combined	9.29 ± 1.18	9.76 ± 1.23	9.18 ± 1.23	7.95 ± 1.13
1X males	10.28 ± 1.51	9.48 ± 0.73	9.08 ± 0.51	8.02 ± 0.89
1X females	9.38 ± 0.81	9.67 ± 1.09	9.28 ± 0.62	8.58 ± 1.05
1X combined	9.83 ± 1.25	9.58 ± 0.89	9.19 ± 0.55	8.30 ± 0.97
3X males	9.80 ± 0.86	9.57 ± 0.74	9.27 ± 0.48	8.32 ± 0.63
3X females	8.90 ± 0.73	9.70 ± 1.03	9.53 ± 0.70	7.98 ± 0.87
3X combined	9.35 ± 0.89	9.63 ± 0.86	9.40 ± 0.59	8.15 ± 0.74
5X males	9.68 ± 0.78	10.07 ± 0.69	9.30 ± 0.57	8.03 ± 0.73
5X females	9.78 ± 0.85	**8.93 ± 0.91**	9.35 ± 0.52	8.00 ± 0.90
5X combined	9.73 ± 0.78	9.50 ± 0.97	9.33 ± 0.52	8.02 ± 0.78

Individual data on p. 796, 797, 809, 810, 822, 823, 835, 836, 848, 849, 861, 862, 874, 875, 887 and 888; Means and Standard Deviations on p. 197, 198 and 202.
P-value for 5X females at 24 hrs postdose: 0.0073 (from p. 196; statistically significantly different from concurrent control values).

H. CLINICAL CHEMISTRY

From p. 21: "Clinical chemistry parameters were...not considered to be adversely affected by treatment with R-28153 spot-on formulation. Alkaline phosphatase (ALP) tended to increase in gender-pooled samples, including Placebo Controls, in all groups

over time but only reached statistical significance at 5X on Day 22. There was no consistent dose dependant response that would make this effect definitely attributable to treatment. Potassium was statistically increased in males at Day 22 at 3X and 5X. Females exhibited an opposite effect, showing a decrease in potassium values at 1X and 5X on Day 22. Because of the low magnitudes and opposite directions of changes between sexes, these changes are not considered to be test substance related. Chloride was increased in pooled samples at 3X on Day 22 but because of the low magnitude of the change, was not considered physiologically relevant."

TABLE 8. Means ± S.D. for Alkaline Phosphatase (U/L)

Group and sex	Week -1 (Pretest)	24 hrs postdose	Day 8	Day 22
Placebo males	70.3 ± 27.9	75.7 ± 14.1	85.5 ± 23.9	92.8 ± 22.6
Placebo females	68.7 ± 21.2	77.5 ± 16.9	77.0 ± 23.2	77.2 ± 33.0
Placebo combined	69.5 ± 23.6	76.6 ± 14.9	81.3 ± 22.9	85.0 ± 28.2
1X males	70.0 ± 21.4	77.0 ± 20.4	84.8 ± 27.6	88.2 ± 20.6
1X females	66.3 ± 19.2	82.8 ± 26.3	97.7 ± 36.6	90.2 ± 26.7
1X combined	68.2 ± 19.5	79.9 ± 22.7	91.3 ± 31.6	89.2 ± 22.8
3X males	77.8 ± 13.0	75.7 ± 28.4	82.5 ± 19.1	102.5 ± 6.4
3X females	63.7 ± 14.2	75.2 ± 16.2	77.3 ± 15.1	91.7 ± 31.4
3X combined	70.8 ± 14.9	75.4 ± 22.1	79.9 ± 16.7	97.1 ± 22.3
5X males	76.7 ± 10.4	84.2 ± 18.2	106.2 ± 38.4	110.5 ± 18.3
5X females	66.2 ± 24.7	83.7 ± 25.2	97.5 ± 33.2	121.3 ± 44.6
5X combined	71.4 ± 18.9	83.9 ± 21.0	101.8 ± 34.5	115.9 ± 33.0

Individual data on p. 1049, 1050, 1055, 1056, 1061, 1062, 1067, 1068, 1073, 1074, 1079, 1080, 1085, 1086, 1091 and 1092; Means and Standard Deviations on p. 324, 325 and 329. P-value for 5X combined at 22 Days: 0.0025 (from p. 323; statistically significantly different from concurrent control value).

The three highest levels of alkaline phosphatase were observed in three 5X females on Day 22 (#107: 187 U/L; #139: 147 U/L; and #116: 143 U/L). #139 also had a somewhat elevated ALT (value of 58 U/L, although within the "normal" range of 4-90 U/L given in http://www.ahc.umn.edu/rar/RefValues.html) on Day 22. The same reference gives a "normal" range of 3-70 U/L for alkaline phosphatase (ALP), but ALP activity levels are typically much higher in younger animals, and can fluctuate over wide ranges. In humans ALP rises rapidly during the first 4 weeks of life to 5 or 6X normal adult values, then decreases slowly until puberty when there is another increase, followed by a decrease to adult levels at 16-20 years of age.

TABLE 9. Means ± S.D. for Potassium (mEq/L)				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo males	5.35 ± 0.43	6.07 ± 0.79	6.17 ± 0.88	5.08 ± 0.53
Placebo females	6.62 ± 0.76	6.43 ± 1.31	7.55 ± 0.53	6.93 ± 0.85
Placebo combined	5.98 ± 0.88	6.25 ± 1.05	6.86 ± 1.00	6.01 ± 1.18
1X males	6.68 ± 0.72	6.67 ± 1.25	6.83 ± 1.02	6.00 ± 0.75
1X females	6.15 ± 0.54	6.55 ± 0.75	6.82 ± 0.40	**5.50 ± 0.47**
1X combined	6.42 ± 0.66	6.61 ± 0.98	6.83 ± 0.74	5.75 ± 0.65
3X males	6.15 ± 1.03	7.18 ± 0.97	7.32 ± 0.55	**6.55 ± 0.67**
3X females	6.30 ± 0.67	6.58 ± 0.69	7.45 ± 0.84	6.50 ± 1.08
3X combined	6.23 ± 0.83	6.88 ± 0.86	7.38 ± 0.68	6.53 ± 0.86
5X males	6.15 ± 0.75	6.93 ± 1.20	7.10 ± 1.08	**6.40 ± 0.60**
5X females	6.50 ± 0.88	6.48 ± 0.50	6.48 ± 0.73	**5.78 ± 0.34**
5X combined	6.33 ± 0.80	6.71 ± 0.91	6.79 ± 0.94	6.09 ± 0.57

Individual data on p. 1049, 1050, 1055, 1056, 1061, 1062, 1067, 1068, 1073, 1074, 1079, 1080, 1085, 1086, 1091 and 1092; Means and Standard Deviations on p. 294, 295 and 299.
P-values at 22 Days: 3X males: 0.0039; 5X males: 0.0102; 1X females: 0.0020; 5X females: 0.0066 (from p. 293; statistically significantly different from concurrent control values).

Individual potassium values observed in this study ranged from 4.5 to 8.3 mEq/L, with no indication of any dose and/or exposure-related effect.

TABLE 10. Means ± S.D. for Chloride (mEq/L)				
Group and sex	**Week -1 (Pretest)**	**24 hrs postdose**	**Day 8**	**Day 22**
Placebo males	118.3 ± 2.3	118.8 ± 1.8	117.3 ± 1.5	117.8 ± 1.5
Placebo females	120.2 ± 1.9	120.8 ± 2.5	120.5 ± 7.2	119.7 ± 1.6
Placebo combined	119.3 ± 2.2	119.8 ± 2.3	118.9 ± 5.2	118.8 ± 1.8
1X males	119.7 ± 1.8	119.2 ± 1.6	117.2 ± 1.9	118.3 ± 1.6
1X females	118.3 ± 1.5	117.8 ± 1.7	118.5 ± 1.5	118.0 ± 2.2
1X combined	119.0 ± 1.7	118.5 ± 1.7	117.8 ± 1.8	118.2 ± 1.9
3X males	119.2 ± 2.2	118.8 ± 2.9	119.5 ± 0.8	120.5 ± 2.1
3X females	119.5 ± 2.6	120.7 ± 2.3	119.0 ± 2.3	119.8 ± 2.0
3X combined	119.3 ± 2.3	119.8 ± 2.7	119.3 ± 1.7	**120.2 ± 2.0**
5X males	118.5 ± 3.0	120.8 ± 2.2	120.0 ± 1.4	120.7 ± 2.3
5X females	119.7 ± 1.2	119.2 ± 1.6	117.8 ± 2.5	118.7 ± 1.6
5X combined	119.1 ± 2.3	120.0 ± 2.0	118.9 ± 2.2	119.7 ± 2.2

Individual data on p. 1049, 1050, 1055, 1056, 1061, 1062, 1067, 1068, 1073, 1074, 1079, 1080, 1085, 1086, 1091 and 1092; Means and Standard Deviations on p. 302, 303 and 307.
P-value at 22 Days: 3X pooled: 0.0794 (from p. 301; statistically significantly different from concurrent control value).

According to http://www.ahc.umn.edu/rar/RefValues.html a normal reference range for chloride in the cat is 117-129 mEq/L. The means shown above are all within this normal range. Individual values observed in this study ranged from 114 to 134 (the value of 134 was observed in control female #146 on Day 8; the next highest value observed in this study was 124).

I. NECROPSY FINDINGS

As there were no mortalities, there were no necropsy findings.

IV. DISCUSSION

This is the first application for registration that the Agency has received for a cat and kitten spot-on formulation containing R-28153.

According to proposed label directions the product would be applied as a spot-on with the following dosage rates: cats and kittens ≤ 4 kg (up to 9 lbs): 0.8 mL; > 4 kg (> 9 lbs): 1.6 mL.

In this companion animal safety study (MRID 46437616), 4 groups, each containing 12 (6/sex) 53-57 day-old kittens (source: Liberty Research Inc., Waverly, NY; weights on Day -1: males: 0.568 to 0.866 kg; females: 0.566 to 0.855 kg) were treated at 0X (4.0 mL placebo), 1X (0.8 mL spot-on formulation), 3X (2.4 mL spot-on formulation) and 5X (4.0 mL spot-on formulation). Application to each kitten was between the shoulder blades on the dorsal midline; the hair was separated and the appropriate amount of test material was applied to the skin while the dispensing syringe was dragged back slowly distally.

On the day of dosing (Day 1: there was no Day 0) clinical observations were made predose and at 15 minutes, 1, 2 and 3 hours postdose. Otherwise, clinical observations were twice daily, approximately 4 hours apart, from the last 4 days of the acclimation period and then from Days 2 through 28, except on days of neurological and physical examinations (Days -1, 1, 2, 8 and 22).

Kittens were individually weighed on Days -14, -12, -9, -7, -5, -2, -1, and then postdose on Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 and 29. Food consumption is reported (g/kitten/day) for weeks -1, 1, 2, 3 and 4. Blood samples were taken (from the jugular vein) following overnight fasts once pretest (Week -1) and then on Days 2 (24 hours postdose), 8 and 22. If redraws were necessary these were collected approximately 48 hours after the initial draws.

All kittens survived and there was no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed.

The only effect seen was salivation, observed in a number of kittens (including some in the placebo group) at 1 hour postdose with the following incidences: placebo control: 3/6M, 2/6F; 1X: 0/6M, 0/6F; 3X: 1/6M, 1/6F; 5X: 1/6M, 3/6F. As the highest incidence of salivation was observed in the placebo controls, it can be ascribed to one or more of the inerts/solvents in this formulation.

Sporadic statistically significant differences involving hematology and clinical chemistry parameters (leukocyte counts, MCHC, prothrombin time, alkaline phosphatase activity, potassium and chloride) in gender-pooled samples or in one sex were not biologically relevant, as they were not exposure/dose-related, were generally minimal, and individual values tended to fall within normal ranges. Similar changes in the same parameters were not observed in the adult cat study with this formulation (MRID 46437615)

As no kittens weighing more than 4 kg were tested in this study, labeling should indicate that no more than 0.8 mL should be applied to kittens of 6 months of age.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for 8-week-old kittens, and demonstrates an adequate 5X margin of safety for the proposed use of this formulation at an application of rate of 0.8 mL/dose. While salivation was noted (mostly in the 2-hour period following application) this may have been associated with ingestion from grooming and/or the odor and/or taste of the formulation or its solvents. The proposed label includes the statement: "Ingestion may result in a brief period of salivation; this is not a sign of toxicity but a response to the taste of the product and disappears without treatment." This statement should be modified to something like: "Ingestion or exposure may result in a brief period of salivation; this response should disappear without treatment." The registration of this product could be made conditional on the label inclusion of this modified statement.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D314413
2. **PC CODE:** 281250 [Metaflumizone, R 28153; BAS 320 I]
3. **CURRENT DATE:** October 3, 2005
4. **TEST MATERIAL:** 20% w/v R-28153 spot-on formulation, Lot No. 0381704, a pale yellow liquid with a specific gravity of 1.085 g/mL containing (from p. 429 of MRID 46437615) 20.3% R-28153 (Metaflumizone); consistent with the label declaration for EPA File Symbol 80490-G [Promeris Spot On for Cats] of 18.53% Metaflumizone.

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion Animal Safety/Adult Cats/ MPI Research Inc./Study #817-009 /Sponsor Study #0817-F-US-01-03/ May-19-2004	46437615	Applied on Day 1 to groups of 6M &6F young (173-245 day old) adult cats (M: 2.2-4.5 kg; F: 1.8-3.5 kg) were treated at 0X (4 or 8 mL placebo), 1X (0.8 or 1.6 mL spot-on), 3X (2.4 or 4.8 mL spot-on) or 5X (4 or 8 mL spot-on). Lower doses were for cats <4 kg and higher doses were for >4 kg (1M/group). Application to each cat was between shoulder blades on dorsal midline using a syringe. All cats survived with no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed. Only effect noted was salivation, seen in a number of cats (including some in placebo group) with incidences: 0X: 2/6M, 3/6F; 1X: 1/6M, 2/6F; 3X: 0/6M, 2/6F; 5X: 2/6M, 1/6F. Salivation was seen in a 5X female on Day 2 (day after dosing). Sporadic statistically significant changes in clinical chemistry and hematological parameters were not biologically relevant as most tended to be within normal ranges.	-	A
Companion Animal Safety/Kittens/ MPI Research Inc./ Study #817-010/ Sponsor Study #0817-F-US-03-03/May-11-2004	46437616	Applied on Day 1 to groups of 6M & 6F 53-57 day old kittens (M: 0.568-0.866 kg; F: 0.566-0.855 kg) at 0X (4 mL placebo); 1X: (0.8 mL spot-on); 3X (2.4 mL spot-on); and 5X (4 mL spot-on). All kittens weighed less than 4 kg. Application to each kitten was by syringe to between shoulder blades on dorsal midline. All kittens survived with no indication of any effects on body weight or food consumption. No neurological effects or abnormalities were observed. Only effect noted was salivation, including some in placebo group (0X: 3/6M, 2/6F; 1X: 0/6M, 0/6F; 3X: 1/6M, 1/6F; 5X: 1/6M, 3/6F). Sporadic statistically significant changes in clinical chemistry and hematological parameters were not biologically relevant as most tended to be within normal ranges.	-	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self-Validated**