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Chemical:	**Fipronil**
PC Code:	**129121**
HED File Code	**13000 Tox Reviews**
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB - 1 1995

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Fipronil (0.25% w/v) (Tradename: Frontline) Review of Domestic Animal Safety Study in Kittens

P.C. Code: 129121
DP Barcode: D210698
Case: 040837
Submission: S479528

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer Virginia A Dobozy 1/30/95
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Marion Johnson/Daphne Waldo/PM 10
Registration Division (7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y M Ioannou 1/31/95
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 2/1/95
Toxicology Branch II
Health Effects Division (7509C)

Registrant: Rhone-Merieux, Inc.

Action Requested: Review Domestic Animal Safety Study in Kittens

Recommendation: Toxicology Branch II has reviewed the domestic animal safety study in kittens and finds it acceptable. Toxicology Branch II recommends that the request for a EUP for testing in veterinary hospitals be granted for adult and juvenile cats and dogs.

Data Summary

Study Title: Domestic Animal Safety Study of RM1601C Topical Spray in Juvenile Cats

Material Tested: RM1601C (0.25% fipronil); Trade Name: Frontline

In this domestic animal safety study (MRID # 434449-04), 4 male and 4 female domestic short hair kittens (≤ 8 weeks of age) were administered a single topical treatment of RM1601C (0.25% fipronil) at 6 ml/kg (recommended dosage) once every month for three months. Another group of 6 male and 6 female kittens were treated in a like manner with five times the recommended dosage. A group of 4 male and 4 female kittens served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. The following parameters were evaluated: physical examinations, clinical observations, body weight, food consumption, hematology, clinical chemistry and gross necropsy examination of the abdominal cavity. There was no evidence of a treatment-related effect on any of the parameters. The study demonstrated that the RM1601C (0.25%) has at least a 5X margin of safety in kittens.

Core Classification: Acceptable

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 1/31/95
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 1/31/95
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Domestic Animal Safety Study/Cats (86-1)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 434449-04
TEST MATERIAL:	RM1601C (Fipronil, 0.25%) Trade Name: Frontline
STUDY NUMBER:	WEL NO. 94424
TESTING FACILITY:	White Eagle Toxicology Laboratories Doylestown, PA
SPONSOR:	Rhone Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Domestic Animal Safety Study of RM1601C Topical Spray in Juvenile Cats
AUTHORS:	Edward Schwartz, VMD, PhD
REPORT ISSUED:	November 4, 1994

EXECUTIVE SUMMARY: In this domestic animal safety study (MRID # 434449-04), 4 male and 4 female domestic short hair kittens (≤ 8 weeks of age) were administered a single topical treatment of RM1601C (0.25% fipronil) at 6 ml/kg (recommended dosage) once every month for three months. Another group of 6 male and 6 female kittens were treated in a like manner with five times the recommended dosage. A group of 4 male and 4 female kittens served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. The following parameters were evaluated: physical examinations, clinical observations, body weight, food consumption, hematology, clinical chemistry and gross necropsy examination of the abdominal cavity. There was no evidence of a treatment-related effect on any of the parameters. The study demonstrated that the RM1601C (0.25% fipronil) has at least a 5X margin of safety in kittens.

Core Classification: Acceptable

Background

This study was previously submitted in preliminary form and was not reviewed because of missing or confusing information. (See July 7, 1994 memo from Virginia Dobozy to Robert Brennis/Daphne Waldo/PM 10). There was also a concern that the 5X dose was not achieved using the single application method.

I. MATERIALS

A. Test Material

Name: RM 1601C
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-4-((1R,S)-(trifluoromethyl)sulphinyl)-1-H-pyrazole-3-carbonitrile
Purity: 0.25% w/v
Batch Number: H07.03
Description: Clear liquid
Storage Conditions: Ambient temperature

Vehicle Control: Isopropyl alcohol

The test material was supplied as a spray in a 100 ml bottle.

B. Administration: topical

C. Test Animals

Species: Domestic short hair cats
Source: Liberty Research, Waverly, N.Y.
Age: Mean age less than 8 weeks on Day 0 (initiation of study)
Weight: Mean - approximately 2 lbs. on Day 0
Housing: Two per cage until 12 weeks of age and then individually on days when treated
Environmental Conditions: Compiled with *Guide for the Care and Use of Laboratory Animals*
Food and Water: Purina Feline Diet #5003 with powdered milk until 12 weeks of age; dry diet alone thereafter
Acclimation Period: One week

II. METHODS

A. Dosage and Administration

Twenty-eight cats were divided into the following groups using a computer generated table of random numbers.

Group No.	Group	Dose (ml/kg)	Number of Animals Males	Females
1	control	30	4	4
2	1X	6	4	4
3	5X	30	6	6

The sprays were applied once monthly for three months. The projected dose was divided into five equal portions which were then applied to five different areas of the dorsum of each kitten. Approximately 30 seconds were allowed between each application to observe for any dripping or run-off. The study report states that because of the nature of the product formulation [redacted] the product evaporated rapidly. Occasional dripping (estimated at approximately 0.5 ml) was "wiped up" with remaining undosed areas such as tail or paws. Six of the eight animals in the 1X dose received doses in excess of 10% over the calculated theoretical dose on Day 0, however the total dose for these animals remained within 10% of the expected dose.

B. Experimental Design

The study protocol required the following observations and examinations at the indicated times or frequencies.

physical examinations - one week prior to dosing and at 13 weeks
clinical observations - twice daily
body weights - day -1 and weekly thereafter
food consumption - estimated twice daily beginning day -3 until 12 weeks of age and once daily thereafter
hematology and clinical chemistry - weeks -1, 2, 4, 6, 8, 10 and 13 on all animals
necropsy examinations - gross examination of the abdominal cavity of all animals

C. Pathological Parameters

Hematology

The CHECKED (X) hematology parameters were examined.

X Hematocrit (HCT)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc. (MCHC)
X Mean corpuscular volume (MCV)
X Hemoglobin (HGB)
__ Leukocyte count (WBC)
X Erythrocyte count (RBC)
X Platelet count
X Activated partial thromboplastin time

Clinical Chemistry

The CHECKED (X) clinical chemistry evaluations were done.

X Glucose	X Total Protein
X Blood urea nitrogen	X Albumin
X Creatinine	X Globulin
X SGPT/ALT	X A/G Ratio
X SGOT/AST	X Sodium
X Alkaline phosphatase	X Chloride
X Total bilirubin	X Calcium
X Gamma glutamyl transferase	X Phosphorus

Necropsy

All animals were sacrificed with pentobarbital after at least 30 days following the last dose. The abdominal cavity was examined; the livers were removed and retained in fixative for future microscopic examination.

D. Statistical Analyses

Group means were compared by the one way analysis of variance (ANOVA) procedure. When significant differences ($p \leq 0.05$) among the means were observed, the Dunnett's test was used to determine which mean was different from the control.

E. Compliance

Signed statements of compliance with the Good Laboratory Practices regulations and Quality Assurance were included. The registrant claims no data confidentiality.

III. RESULTS

A. Clinical Observations

No treatment-related clinical signs were observed.

B. Body Weight and Food Consumption

There were no statistical differences in body weight. Body weight gain was not analyzed but gains in the treated animals were relatively comparable to that of the controls. There were some statistical differences in food consumption between the treated and control group but they were sporadic.

G. Clinical Pathology

Hematology

There were only sporadic statistical differences between the treated and control groups.

Clinical Chemistry

Statistical differences between the treated and control groups were minor and not biologically significant. The SGPT levels of some treated animals (1X and 5X groups) exceeded the laboratory reference values on some occasions, however group means were comparable to the controls.

H. Gross Pathology

There was no evidence of any treatment-related changes on gross examination of the abdominal cavity.

IV. CONCLUSIONS

In this domestic animal safety study (MRID # 434449-04), 4 male and 4 female domestic short hair kittens (≤ 8 weeks of age) were administered a single topical treatment of RM1601C (0.25% fipronil) at 6 ml/kg (recommended dosage) once every month for three months. Another group of 6 male and 6 female kittens were treated in a like manner with five times the recommended dosage. A group of 4 male and 4 female kittens served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. The following parameters were evaluated: physical examinations, clinical observations, body weight, food consumption, hematology, clinical chemistry and gross necropsy examination of the abdominal cavity. There was no evidence of a treatment-related effect on any of the parameters. The final report for this study adequately addresses the deficiencies in the preliminary study report. The study demonstrated that the RM1601C (0.25% fipronil) has at least a 5X margin of safety in kittens.