

US EPA ARCHIVE DOCUMENT



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

011677
Sept. 9/15/95

REVIEWER

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Fipronil (RM 1601C) - Review of Domestic
Animal Safety Study in Puppies

P.C. Code: 129121
DP Barcode: D214998
Case: 014261
Submission: S486457

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TO: Rick Keigwin/Ann Sibold/PM 10
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head *Y.M. Ioannou 9/12/95*
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Karl P. Baetcke, Ph.D., Acting Branch Chief
Toxicology Branch II
Health Effects Division (7509C) *KA 9/15/95*

Registrant: Rhone-Merieux, Inc.

Action Requested: Review Domestic Animal Safety Study in Puppies

Recommendation: Toxicology Branch II has reviewed the domestic
animal safety study in puppies with RM 1601C
(0.29% a.i.) and finds it unacceptable. (See
STUDY DEFICIENCIES.) The study may be upgraded
with satisfactory responses to questions
concerning test formulation, dosage, treatment
of replacement animals and necropsy results.



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DATA SUMMARY

Domestic Animal Safety Study (86-1): "Domestic Animal Safety Study of RM1601C Topical Spray in Juvenile Dogs": MRID # 434449-05

Material Tested: RM 1601C Topical Spray (0.25% w/v fipronil)

Groups of four or six beagle dogs (\approx 8 weeks old) per sex were administered a single treatment of RM 1601C Topical Spray (0.25% w/v fipronil) at dosages of 6 ml/kg (1X recommended dose) or 30 ml/kg (5X recommended dose), respectively. A control group of four animals/sex was treated with the vehicle (isopropyl alcohol) at 30 ml/kg (5X). A total of three monthly treatments were administered. The following parameters were evaluated: clinical observations, body weight, food consumption, hematology and clinical chemistry. Two control group males and one female in the 5X group died during the study; the cause of death was reported as parvovirus infection. There was no evidence of a treatment-related effect on any of the parameters.

Classification: The study is unacceptable because of questions concerning the test formulation, dosage, treatment of replacement animals and necropsy results. (See STUDY DEFICIENCIES.) The study may be upgraded with satisfactory responses to these questions.

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. *Virginia A Dobozy 9/12/95*
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M. Ioannou 9/12/95*
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Domestic Animal Safety Study/Dogs (86-1)
EPA I.D. NUMBERS: P. C. CODE: 129121
MRID NUMBER: 434449-05
TEST MATERIAL: RM 1601C
Synonym: Fipronil
STUDY NUMBER: WEL No. 94423
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 Dogs
AUTHOR(S): Edward Schwartz, VMD, PhD
REPORT ISSUED: September 23, 1994

EXECUTIVE SUMMARY: In a domestic animal safety study (MRID # 434449-05), groups of four or six beagle dogs (~ 8 weeks old) per sex were administered a single treatment of RM 1601C Topical Spray (0.25% w/v fipronil) at dosages of 6 ml/kg (1X recommended dose) or 30 ml/kg (5X recommended dose), respectively. A control group of four animals/sex was treated with the vehicle (isopropyl alcohol) at 30 ml/kg (5X). A total of three monthly treatments were administered. The following parameters were evaluated: clinical observations, body weight, food consumption, hematology and clinical chemistry. Two control group males and one female in the 5X group died during the study; the cause of death was reported as parvovirus infection. There was no evidence of a treatment-related effect on any of the parameters.

The study is unacceptable because of questions concerning the test formulation, dosage, treatment of replacement animals and necropsy results. (See STUDY DEFICIENCIES.) The study may be upgraded with satisfactory responses to these questions.

I. MATERIALS

A. Test Material

Name: RM 1601C Topical Spray (250 ml bottle)

Synonym: Fipronil

Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethylsulphonylpyrazole

Purity: 0.25% w/v fipronil

Batch Number: H07.03

Description: Clear liquid

Storage Conditions: Not provided

Vehicle Control: Isopropyl alcohol

The study report states that the test material was stored under ambient conditions for 4.5 months prior to the initiation of the study. Stability studies have shown the product to be stable for at least six months.

B. Administration: dermal

C. Test Animals

Species: Beagle dogs

Source: White Eagle Laboratories, Inc.

Age: Less than eight weeks at initiation of treatment

Weight: Males - approximately 3 kg; Females - approximately 2.5 kg at initiation of treatment

Housing: Both individually and in groups¹

Environmental Conditions: Not provided

Food and Water: Purina Certified Canine Diet #5007 wetted with powdered milk until approximately 13-14 weeks and then dry diet for the duration of the study; water was provided *ad libitum*

Acclimation Period: One week

II. METHODS

A. Dosage and Administration

Fourteen dogs of each sex were randomly assigned to three groups as follows:

¹ The dogs were housed two per cage except on the days of product application when they were housed individually. Additionally, dogs 3 and 28 were housed individually after the death of their cage mates and the replacement with younger animals (33, 34) that were initially started on wet diet.

Group	Number		Dose of RMI 1601
	Males	Females	
Control	4	4	0 (30 ml/kg vehicle)
1X	4	4	6 ml/kg
5X	6	6	30 ml/kg

Three treatments were administered at 30 day intervals. The groups were treated in ascending order (groups 1-2-3). The projected dose was divided into five equal portions which were applied to five discrete areas of the dorsum of each dog. Thirty seconds were allowed between each application to observe for dripping or any run-off. The protocol called for the 5X application to be made in 5 equal increments allowing the product to dry between applications. The study report states that this deviation occurred in order to allow an efficient amount of time for complete dosing of the subjects. Because of the high alcohol content of the formulation, the product evaporated quickly and therefore, run-off was minimal. Occasional dripping (≈ 0.5 ml) was "wiped up" with remaining undosed areas such as ears, tail or paws. (This deviation was considered acceptable for a similar study in cats; see MRID # 434449-04). One dog in the control group received 30.38 ml less than the calculated dose on Day 61 due to a technical error.

B. Experimental Design

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

physical examinations - weeks -1 and 13
 clinical observations - twice daily
 body weights - day -1 and weekly thereafter
 food consumption - qualitatively estimated² daily beginning on
 day - 3
 hematology and clinical chemistry - weeks -1, 2, 4, 6, 8, 10 and 13
 on all animals

C. Pathological Parameters

Hematology

The following hematology parameters were examined.

Hematocrit (HCT)	Hemoglobin (HGB)
Leukocyte differential count	Leukocyte count (WBC)
Mean corpuscular HGB (MCH)	Erythrocyte count (RBC)
Mean corpuscular HGB conc. (MCHC)	Platelet count
Mean corpuscular volume (MCV)	Prothrombin time
Activated Partial Thromboplastin Time	

² Food consumption was estimated using the following scale of the amount consumed: 1 = 1-24% ; 2 = 25-49% ; 3 = 50-74% ;
 4 = 75-100%.

Clinical Chemistry

The following clinical chemistry evaluations were done.

Glucose	Total Protein
Blood Urea Nitrogen	Albumin
Creatinine	Globulin
SGPT/ALT	A/G Ratio
SGOT/AST	Sodium
Alkaline Phosphatase	Chloride
Total Bilirubin	Calcium
Gamma Glutamyl Transferase	Phosphorus

D. Statistical Analyses

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

E. Compliance

A signed statement indicating that the study was conducted in compliance with the GLP regulations, along with a Quality Assurance Report were submitted. A signed Statement of Data Confidentiality Claims indicates no confidentiality is claimed by the registrant.

III. RESULTS

A. Mortality

Two control group males and one 5X group female died during the study. According to the clinical observations table on page 23, dog # 3M (control) died on day 62; 4M (control) died on day 22; and 27F died on day 16. All three had respiratory signs prior to death.

The study report (page 14) states that the findings on gross necropsy were compatible with canine parvoviral infection. Gross respiratory system lesions (mottled lungs, frothy trachea &/or fluid in thoracic cavity) were found in all three dogs. Gastrointestinal lesions (intestines reddened or red streaked) were observed in two dogs.

B. Clinical Observations

In surviving animals, respiratory signs (ocular and nasal discharge, congestion, dyspnea) were occasionally reported in the control and treated dogs.

C. Body Weights

Mean weekly body weights of the treated and control groups were

D. Food Consumption

The qualitative estimates of food consumption of the treated and control groups appear to be comparable. However, the study report did not specify if the dogs were fed on a per weight or *ad libitum* basis.

E. Clinical Pathology

Hematology and Clinical Chemistry

There were very few statistically significant differences between the treated and control values for the clinical pathology parameters measured. None appeared to be biologically significant.

IV. STUDY DEFICIENCIES

1. The formulation used in the study contained 0.25% w/v fipronil, whereas the proposed label indicates that the product contains 0.29% w/w fipronil. The registrant should explain this inconsistency and the difference in the amount of active ingredient.

2. The dosage used for the 1X group in this study was 6 ml/kg. The proposed product label states that the recommended dosage is approximately 3 to 6 pumps per pound of a small bottle and 1 to 2 pumps per pound for the large bottle. In parentheses after both dosages is the notation "1/2 to 1 oz of spray to treat an average size cat and 1 to 2 oz of spray to treat a 25 pound dog". The registrant should clarify how the recommended dosage on the label equates to the 1X dosage used in the study.

3. Clarification is needed concerning the replacement of the animals which died. According to the clinical observations table on page 23, dog # 3M died on Day 62, 4M on Day 22 and 27F on Day 16. Dog 4M was replaced by 34M and 27F by 33F. However, it is unclear how many treatments these replacement animals received. The dosage compliance table on page 20 shows that both of the replacement dogs received treatments on days 0, 31 and 61. However, the original dogs did not die until after they had received one treatment. In addition, data are presented for most of the parameters (body weight, food consumption and clinical pathology) for dogs # 34M and 27F from the pretest time period when they should not have been added to the study until after days 16 and 22.

4. Individual necropsy reports should have been provided for each of the dogs which died.

V. CONCLUSIONS

Groups of four or six beagle dogs (\approx 8 weeks old) per sex were administered a single treatment of RM 1601C Topical Spray (0.25% w/v fipronil) at dosages of 6 ml/kg (1X recommended dose) or 30 ml/kg (5X recommended dose), respectively. A control group of four animals/sex was treated with the vehicle (isopropyl alcohol) at 30 ml/kg (5X). A total of three monthly treatments were administered. The following parameters were evaluated: clinical observations, body weight, food consumption, hematology and clinical chemistry. Two control group males and one female in the 5X group died during the study; the cause of death was reported as parvovirus infection. There was no evidence of a treatment-related effect on any of the parameters.