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

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JUN 7 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fipronil - Review of Acute Toxicity Studies to Support EUP for Domestic Animal Product (0.25% fipronil)

PC Code: 129121
DP Barcode: D202243
Case: 040837
Submission: S458528

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer Virginia A Dobozy 5/19/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Robert Brennis/Daphne Waldo/PM 10
Registration Division (7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
Health Effects Division (7509C) 5/19/94

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) 5/23/94

Registrant : Rhone Merieux Inc.

Action Requested: Review six acute toxicity studies submitted to support an EUP for the animal spray.

Recommendation: Toxicology Branch II has completed its review of the above referenced studies. All of the studies are acceptable, except for the dermal sensitization study. This study may be upgraded with the submission of historical positive control data. As indicated in an April 19, 1994 memo, our recommendation regarding an EUP for this formulation (when the toxicology data base is complete) is for limited testing in adult dogs.

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DATA REVIEW

All of the studies were conducted with the 0.25% formulation.

Acute Oral Toxicity/Rat (81-1): MRID # 431211-04

The acute oral LD_{50} for RM 1601C (0.25% fipronil) was greater than 5000 mg/kg for male and female rats.

Toxicity Category: IV

Classification: Acceptable

Acute Dermal Toxicity/Rat (81-2): MRID # 431211-05

The acute dermal LD_{50} for RM 1601C (0.25% fipronil) was greater than 2000 mg/kg for male and female rats.

Toxicity Category: III

Classification: Acceptable

Acute Inhalation Toxicity/Rat (81-3): MRID # 431211-06

The acute inhalation LC_{50} for RM 1601C (0.25% fipronil) was greater than 5.06 mg/l.

Toxicity Category: IV

Classification: Acceptable

Primary Eye Irritation/Rabbit (81-4): MRID # 431211-07

The study demonstrated that RM 1601C (0.25% fipronil formulation) is an ocular irritant in rabbits.

Toxicity Category: III

Classification: Acceptable

Primary Dermal Irritation/Rabbit (81-5): MRID # 431211-08

The study demonstrated that RM 1601C (0.25% fipronil formulation) is not a dermal irritant in rabbits.

Toxicity Category: IV

Classification: Acceptable

Dermal Sensitization/Guinea Pig (81-6): MRID # 431211-09

The chemical's potential to produce dermal sensitization could not be judged with assurance due to the lack of a positive control in the study.

Classification: Unacceptable

Labeling Issues

The pesticide labeling regulations, specifically 40 CFR 156.10 (i)(B), provide that certain precautionary statements appear on the label if skin or local eye effects are in toxicity category III. Statements on the draft label do reflect the acute toxicity of this chemical.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 5/10/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y M Ioannou 5/18/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral Toxicity/Rats (81-1)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-04
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	10798 TAR
TESTING FACILITY:	Centre International De Toxicologie (C.I.T.) Miserey, France
SPONSOR:	Rhone-Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Acute Oral Toxicity in Rats
AUTHOR(S):	Jack Clouzeau
REPORT ISSUED:	September 21, 1993

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 431211-04), groups of five male and five female Sprague-Dawley rats were administered single oral doses of either RM 1601C (0.25% fipronil) or the excipient of the formulation at a dosage of 5000 mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There was one mortality in the male excipient group but none with the test substance. Clinical signs of toxicity were similar with both treatments. **The acute oral LD_{50} for RM 1601C (0.25% fipronil) was greater than 5000 mg/kg for male and female rats.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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I. MATERIALS

A. Test Material

Name: RM 1601C, 0.25% Spray Formulation
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 0.242% fipronil
Batch Number: G 0901
Description: Colorless liquid
Storage Conditions: At 4°C and protected from light

Excipient: Identified as [redacted] in a confidential attachment.

B. Test Animals

Species: Sprague-Dawley rats
Source: Iffa Credo, L'Arbresle, France
Age: 6 weeks old on the day of treatment
Weight: 171 ± 4 g for males and 143 ± 7 g for females on day of treatment
Housing: Four to seven/sex/cage during the acclimation period; 5/sex/cage during the treatment period
Environmental Conditions: Temperature: 22 ± 3° C
Relative Humidity: 50 ± 20%
Photoperiod: 12 hours light/dark
Air changes: 13 cycles/hour
Food and Water: A04 C pelleted diet and tap water *ad libitum*
Acclimation Period: Five days

II. METHODS

Groups of five males and five females were treated with single oral doses of 5000 mg/kg (limit dose) of either RM 1601C or the formulation's excipient. The doses were adjusted taking into consideration the specific gravity of the formulation (0.854) and the excipient [redacted] The treatments were administered using a stainless steel round-tipped probe fitted to a glass syringe. The animals were observed frequently for mortality and clinical signs of toxicity on Day 1 (day of dosing). For the remainder of the study, the animals were observed twice daily for mortality and once daily for clinical signs of toxicity. Body weights were recorded just before administration and on Days 5, 8 and 15. Surviving animals were sacrificed on Day 15. All animals were subjected to a gross necropsy.

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III. RESULTS

Mortality

One male in the excipient group died on Day 3 of the study. There were no deaths in the animals treated with the test substance.

Clinical Signs

The clinical signs with the test substance and the excipient were almost identical. Sedation and dyspnea were observed between 15 minutes and 2 hours after treatment in all animals, coma after 4 hours and then hypokinesia after 24 - 72 hours.

Body Weight

There was an increase in the mean body weights of all the groups, however some individual animals lost weight during the study.

Gross Necropsy

There were no significant findings on gross necropsy.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) statement indicating that confidential data had been removed to a confidential appendix.

V. CONCLUSIONS

The acute oral LD_{50} for RM 1601C (0.25% fipronil) was greater than 5000 mg/kg for male and female rats.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 5/11/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 5/11/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity/Rats (81-2)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-05
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	9651 TAR
TESTING FACILITY:	Centre International De Toxicologie (C.I.T.) Miserey, France
SPONSOR:	Rhone-Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Acute Dermal Toxicity in Rats
AUTHOR(S):	Jack Clouzeau
REPORT ISSUED:	April 6, 1993

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 431211-05), a group of five male and five female Sprague-Dawley rats were administered a single dermal dose of RM 1601C (0.25% fipronil) at a dosage of 2000 mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There were no deaths nor clinical signs of toxicity. **The acute dermal LD_{50} for RM 1601C (0.25% fipronil) was greater than 2000 mg/kg for male and female rats.**

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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I. MATERIALS

A. Test Material

Name: RM 1601C, 0.25% Spray Formulation
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 0.242% fipronil
Batch Number: G 0901
Description: Colorless liquid
Storage Conditions: At 4°C

B. Test Animals

Species: Sprague-Dawley rats
Source: Iffa Credo, L'Arbresle, France
Age: 8 weeks old on the day of treatment
Weight: 275 ± 8 g for males and 217 ± 10 g for females on day of treatment
Housing: Four to seven/sex/cage during the acclimation period; individually during the study
Environmental Conditions: Temperature: 22 ± 3° C
Relative Humidity: 50 ± 20%
Photoperiod: 12 hours light/dark
Food and Water: A04 C pelleted diet and tap water *ad libitum*
Acclimation Period: Five days

II. METHODS

The day before treatment, an area 6 X 8 cm on the dorsum was clipped. On the day of treatment, the test substance was applied at a dosage of 2000 mg/kg to an area of skin representing approximately 10% of the animal's body surface (5 X 7 cm for males and 5 X 6 cm for females). The area was covered with a gauze patch and a semi-occlusive dressing for 24 hours. The animals were observed frequently on the day of administration for mortality and clinical signs of toxicity. Observations for the remainder of the 14-day observation period were made once daily for clinical signs of toxicity and twice daily for mortality. Body weights were measured just before application of the test substance and on days 5, 8 and 15. On the 15th day of the study, the animals were sacrificed using CO_2 inhalation and gross necropsies were performed.

III. RESULTS

There were no deaths nor clinical signs of toxicity. Body weight gain was comparable to historical control animals from this laboratory. There were no abnormalities on gross necropsy.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) statement indicating that confidential data had been removed to a confidential appendix.

V. CONCLUSIONS

The acute dermal LD_{50} for RM 1601C (0.25% fipronil) was greater than 2000 mg/kg for male and female rats.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A. Dobozy 5/19/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 5/19/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation/Rats (81-3)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-06
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	IRI 652751
TESTING FACILITY:	Inveresk Research International Tranent, Scotland
SPONSOR:	Rhone Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Acute Inhalation Study in Rats
AUTHOR(S):	S.A. Robinson
REPORT ISSUED:	May 26, 1993

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 431211-06), five male and five female Sprague Dawley rats per group were exposed to atmospheric concentrations of either RM 1601C (0.25% fipronil formulation) or the excipient in the formulation for four hours. The animals were observed for mortality and clinical signs of toxicity during the exposure and the 14-day post-exposure observation period. No animals died during the exposure cr observation period. The only clinical sign observed was decreased respiratory rate in both of the groups during the exposure. **The acute inhalation LC_{50} for RM 1601C (0.25% fipronil) was greater than 5.06 mg/l.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-3) for an acute inhalation study in rats.

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I. MATERIALS

A. Test Material

Name: RM 1601C
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 0.242%
Batch Number: G 09 01
Description: Not stated
Storage Conditions: In the dark at +4° C

Excipient: Identified as [redacted] in a confidential attachment.

B. Test Animals

Species: Sprague Dawley rats
Source: Charles River (UK) Limited, Kent, England
Age: Not stated
Weight: 111-121 g at the time of arrival
Environmental Conditions: Temperature: 20 ± 2° C
Humidity: 50 ± 15%
Photoperiod: 12 hours light/dark
Air changes: 15-20 per hour
Housing: Five per cages except during exposure when housed individually
Food and Water: Rat and Mouse (Modified) No. 1 Diet SQC Expanded and tap water *ad libitum* except during exposure
Acclimation Period: Four days

II. METHODS

Exposure Chamber

The aluminum exposure chamber had a volume of approximately 45.0 liters and was located inside an extract cabinet. Air from the chamber was vented through a duct which was connected to a metered vacuum system by way of a high efficiency filter. The animals were held in a tapered restraint tube which fitted into the exposure chamber so that only the snout was exposed to the test atmospheres.

Atmosphere Generation and Monitoring

The test atmospheres were generated using a Gilson pump to continuously meter the test substances through a Schlick atomizer at the top of the exposure chamber. Concentrations within the chamber were controlled by adjusting the rate of feed of the test materials and the air flow to the atomize .

The concentration of the chemical in the test atmosphere was determined gravimetrically on five occasions during the four-hour exposure period. Samples were collected in sorbent tubes positioned

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in a port in the exposure chamber at the animal's breathing zone. The test atmosphere was drawn through the tubes at a rate of approximately 1.0 l/min via a gas meter and vacuum pump. The tubes were weighed before and after each sampling to calculate the difference by weight of the test material which was then divided by the sample air volume to determine concentration.

The nominal concentration was calculated by dividing the weight of the test material delivered by the volume of air which passed through the chamber during the exposure period.

A Marple Cascade Impactor was used to determine the particle size distribution of the test atmosphere twice during the exposure period. The device was positioned at the animal's breathing zone and air was sampled at a rate of 2 l/min. The impaction substrates for each stage were weighed before and after each sampling; the weight difference was the mass of particles in the size range of each impactor stage. The total weight of the particles collected and the percent of each particle size range was calculated.

The temperature, humidity and air flow within the chamber were monitored every 30 minutes.

Animal Treatment

Five male and five female rats per group were administered a four-hour snout-only exposure of either RM 1601C or the formulation's excipient. Observations for mortality and clinical signs of toxicity were made every 30 minutes during the exposure and then twice daily during the 14-day observation period. The animals were weighed prior to exposure and on Days 2, 3, 4, 7, 10 and 14 post-exposure. At the end of the study, all the surviving animals were sacrificed and necropsied. The lungs of each animal were weighed and lung to body weight ratios were calculated.

III. RESULTS

Test Atmosphere

Air flow within the chamber was a constant 15.1 l/min for both the test substance and the excipient. The average temperature within the chamber was 22° C for the test substance and 23° C for the excipient. There were great variations in the percent relative humidity values for both groups with the mean being 30% and 46% for the test substance and excipient groups, respectively.

The nominal concentrations of the test material and excipient groups were 5.06 and 4.67 mg/l, respectively. The mean gravimetric concentrations based on five samples were 6.19 (± 0.90) mg/l and 5.66 (± 3.30) mg/l for the test material and excipient, respectively. The study report states that the higher values obtained for the gravimetric estimation were due to background moisture content of the chamber atmosphere, therefore the achieved chamber concentrations quoted in the report are based on the

nominal concentrations.

The mean percentages of particles less than 3.5 μm were 99.29% and 98.85% for the test material and excipient groups, respectively. Greater than 95% of the particles were < 1 μm in size.

Test Animals

No animals died during the exposure or observation periods. The only clinical sign observed was a slightly decreased respiration rate in both of the groups during the exposure.

All the animals gained weight normally over the course of the study. On necropsy, the relative weights of the lungs of the treated animals was slightly elevated in comparison to the excipient group.

IV. COMPLIANCE

Signed statements of Quality Assurance and compliance with the Good Laboratory Practice regulations were submitted by the testing facility. The sponsor submitted a statement indicating that confidential material had been removed to a confidential appendix.

V. STUDY DEFICIENCY

Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) values were not calculated for the test atmosphere. However, from Table 3 (page 27), it is evident that the values would have been within acceptable ranges.

V. CONCLUSIONS

The acute inhalation LC_{50} for RM 1601C (0.25% fipronil) was greater than 5.06 mg/l.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-3) for an acute inhalation study in rats.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 5/2/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 5/18/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation/Rabbits (81-4)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-07
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	9653 TAL
TESTING FACILITY:	Centre International De Toxicologie (C.I.T.) Miserey, France
SPONSOR:	Rhone-Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Primary Eye Irritation in Rabbits
AUTHOR(S):	Jack Clouzeau
REPORT ISSUED:	April 6, 1993

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID # 431211-07), 0.1 ml of either RM 1601C (0.25% fipronil formulation) or the excipient of the formulation was instilled into the conjunctival sac of three male New Zealand white rabbits. The eyes were evaluated and scored for ocular irritation at 1 hour, 24, 48 and 72 hours post-instillation. There was evidence of irritation to the conjunctiva, cornea and iris which persisted until Day 6 of the study with the test substance. Scores with the excipient were similar, but the lesions were resolved by Day 5.

The study demonstrated that RM 1601C (0.25% fipronil formulation) is an ocular irritant in rabbits.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-4) for an primary eye irritation study in rabbits.

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I. MATERIALS

A. Test Material

Name: RM 1601C, 0.25% Spray Formulation
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 0.242% fipronil
Batch Number: G 0901
Description: Colorless liquid
Storage Conditions: At +4°C

Excipient: Identified as [redacted] in a confidential attachment.

B. Test Animals

Species: Male New Zealand white rabbits
Source: Elevage Cunicole du Val de Selle, Prouzel, France
Age: Not stated
Weight: 2.7 ± 0.1 kg
Housing: Individually in polystyrene cages
Environmental Conditions: Temperature: 18 ± 3° C
Relative Humidity: 50 ± 20%
Photoperiod: 12 hours light/dark
Food and Water: Rabbits sustenance ref. 112C and water *ad libitum*
Acclimation Period: Five days

II. METHODS

A single dose of 0.1 ml of the test material was instilled into the conjunctival sac of the left eye of three male New Zealand white rabbits; an identical dose of the excipient of the formulation was placed into the right eye. The eyes were not rinsed after the applications. Ocular reactions were evaluated at 1 hour, 24, 48 and 72 hours after instillation according to a standard scoring system (see attachment to the DER). The animals were observed for either five or six days post-instillation.

III. RESULTS

At one hour post-instillation, positive scores were recorded for conjunctival chemosis (mean: 2.3 out of possible 4) and redness (mean: 2.0 out of 4) for the test substance group. At 24 hours, there was some improvement in the conjunctival effects (mean: 1.7 for chemosis and 2 for redness), but all animals had iris lesions (mean: 1 of 4) and corneal opacity (mean degree of opacity: 1.3 of 4; mean area of opacity: 2.7 of 4). These scores remained

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essentially unchanged at the 48 hour evaluation. At 72 hours, one of the rabbits still had evidence of irritation including chemosis, redness, iris lesions and corneal opacity. This rabbic also had a whitish purulent discharge from the eyes. At Day 5, the same rabbit had some remaining corneal opacity. There were no ocular lesions by Day 6.

Scores with the excipient were very similar, however the eyes cleared sooner than with the test substance. There were no positive scores by Day 5.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) statement indicating that confidential data had been removed to a confidential appendix.

V. CONCLUSIONS

The study demonstrated that RM 1601C (0.25% fipronil formulation) is an ocular irritant.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-4) for an primary eye irritation study in rabbits.

Page_____ is not included in this copy.

Pages 17 through 18 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 5/6/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I 5/18/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation/Rabbits (81-5)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-08
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	9652 TAL
TESTING FACILITY:	Centre International De Toxicologie (C.I.T.) Miserey, France
SPONSOR:	Rhone-Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Primary Dermal Irritation in Rabbits
AUTHOR(S):	Jack Clouzeau
REPORT ISSUED:	April 6, 1993

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 431211-08), 0.5 ml of either RM 1601C (0.25% fipronil formulation) or the excipient of the formulation was applied to the skin of three male New Zealand white rabbits. The treated areas were evaluated and scored for dermal irritation at 1 hour, 24, 48 and 72 hours post-application. The only evidence of dermal irritation with either group was very slight erythema at 1 hour post-application in one animal in the test substance group.

The study demonstrated that RM 1601C (0.25% fipronil formulation) is not a dermal irritant in rabbits.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for an dermal irritation study in rabbits.

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I. MATERIALS

A. Test Material

Name: RM 1601C, 0.25% Spray Formulation
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 0.242% fipronil
Batch Number: G 0901
Description: Colorless liquid
Storage Conditions: At +4°C

Excipient: Identified as [redacted] in a confidential attachment.

B. Test Animals

Species: Male New Zealand white rabbits
Source: Elevage Cunicole du Val de Selle, Prouzel, France
Age: Not stated
Weight: 2.5 ± 0.1 kg
Housing: Individually in polystyrene cages
Environmental Conditions: Temperature: 18 ± 3° C
Relative Humidity: 50 ± 20%
Photoperiod: 12 hours light/dark
Food and Water: Rabbits sustenance ref. 112C and water *ad libitum*
Acclimation Period: Five days

II. METHODS

One day prior to treatment, the flanks of three male New Zealand white rabbits were clipped. On the day of treatment, a single dose of 0.5 ml of the test material was applied to a 6 cm^2 gauze patch and placed on the right flank of each animal. The left flanks of these animals were treated with the same dose of the formulation's excipient. The patches were covered with a semi-occlusive dressing for 4 hours. The treated areas were observed for evidence of dermal irritation and scored at 1, 24, 48 and 72 hours after the dressings were removed. The animals were not observed after 72 hours if there were no lesions at that time.

III. RESULTS

The only evidence of dermal irritation with either group was very slight erythema at 1 hour post-treatment with the test substance group.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) statement indicating that confidential data had been removed to a confidential appendix.

V. CONCLUSIONS

The study demonstrated that RM 1601C (0.25% fipronil formulation) is not a dermal irritant.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for an dermal irritation study in rabbits.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 5/19/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 5/19/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Sensitization/Guinea Pig (81-6)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 431211-09
TEST MATERIAL:	RM 1601C, 0.25% Spray Formulation Synonym: Fipronil
STUDY NUMBER:	9654 TSG
TESTING FACILITY:	Centre International De Toxicologie (C.I.T.) Miserey, France
SPONSOR:	Rhone-Merieux, Inc. Athens, Georgia
TITLE OF REPORT:	Dermal Sensitization in Guinea Pigs
AUTHOR(S):	Jack Clouzeau
REPORT ISSUED:	May 5, 1993

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID # 431211-09) using a modified Buehler method, groups of five male and five female Dunkin-Hartley guinea pigs received three induction doses of 0.5 ml of RM 1601 C (0.25% fipronil formulation) at weekly intervals. Fourteen days after the last induction application, the animals were challenged with a 0.5 ml dose of the test substance. Similar groups were treated with the formulation's excipient in an identical manner. There was no evidence of dermal irritation with either treatment after the induction or challenge applications, however no positive control chemical was tested.

The chemical's potential to produce dermal sensitization could not be judged with assurance due to the lack of a positive control in the study.

The study is classified as **Unacceptable** and **does not satisfy** the requirements (81-6) for an dermal sensitization study in guinea pigs. The study may be upgraded if historical data are provided for a positive control chemical tested within six months of this study at this laboratory.

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I. MATERIALS

A. Test Material

Name: RM 1601C, 0.25% Spray Formulation
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 0.242% fipronil
Batch Number: G 0901
Description: Colorless liquid
Storage Conditions: At +4°C

Excipient: Identified as [redacted] in a confidential attachment.

B. Test Animals

Species: Dunkin-Hartley guinea pigs
Source: Lebeau Breeding Centre, Gambais, France
Age: Not stated
Weight: 360 ± 14 g for males and 348 ± 16 g for females
Housing: Individually in polystyrene cages
Environmental Conditions: Temperature: 22 ± 3° C
Relative Humidity: 50 ± 20%
Photoperiod: 12 hours light/dark
Food and Water: Guinea-pigs sustenance ref. 106 and water *ad libitum*
Acclimation Period: Five days

II. METHODS

The study was conducted using a modified Buehler method.

Preliminary Study

In a preliminary study to define the Maximum Non-Irritant Concentration, neither 0.5 ml of the test substance nor the excipient, both in their original form, produced evidence of dermal irritation after a 6-hour exposure.

Definitive Study

Induction Procedure -

The left and right flanks of 5 male and 5 female guinea pigs per group were clipped one day (Day -1) before treatment commenced. On Days 1, 8 and 15, 0.5 ml of either the test substance (full concentration) or the excipient was applied to a 4 cm^2 area of the anterior left flank. The treatments were administered "... directly

to the skin on day 1, prepared on a dry compress, on days 8 and 15, and using a 1 ml sterile polypropylene syringe (0.01 ml graduations, Terumo:CML, 77140 Nemours, France) and held in contact with the skin by means of a 4 cm^2 dressing...". A dry compress was applied to the anterior right flank to serve as a control. An adhesive plaster was placed around the trunk of the animals for 6 hours. Twenty-four hours after each induction application, the treated areas were evaluated for signs of dermal irritation (erythema and eschar formation and edema) and scored.

Challenge Procedure -

On Day 29, 2 weeks after the last induction application, a challenge dose of 0.5 ml of the test substance (full concentration) was applied to the posterior right flank of all animals; 0.5 ml of the excipient was applied to the posterior left flank. The challenge areas were scored for dermal irritation at 24 and 48 hours after the applications.

III. RESULTS

There was no evidence of dermal irritation at any of the induction or challenge evaluation periods.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) statement indicating that confidential data had been removed to a confidential appendix.

V. STUDY DEFICIENCY

There was no positive control in the study to assess the ability of the test system to detect dermal sensitizing chemicals. The study may be upgraded if historical data are provided for a positive control chemical tested within six months of this study at this laboratory.

VI. CONCLUSIONS

The chemical's potential to produce dermal sensitization could not be judged with assurance due to the lack of a positive control in the study.

The study is classified as **Unacceptable** and **does not satisfy** the requirements (81-6) for an dermal sensitization study in guinea pigs.