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

JUN 7 1994

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: M&B 46030 (Fipronil) - Review of Toxicology Data for an EUP/temporary tolerance for use on field corn

PC Code: 129121
DP Barcode: D197450
Case: 285247
Submission: S454829

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 Y M Ioannou 5/19/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) M van Gemert 5/20/94

Registrant: Rhone-Poulenc AG Company

Action Requested: Determine if the toxicology data base for M&B 46030 (Fipronil) is adequate for an EUP/temporary tolerance for use on field corn

Recommendation: Toxicology Branch II recommends that the temporary tolerance for fipronil should not be granted based on the potential of this chemical for carcingenicity and neurotoxicity. (See DISCUSSION.) Furthermore, Toxicology Branch II recommends that an EUP with crop destruct be granted when the data gaps for the acute toxicity studies on fipronil technical and 1.6% formulation are fulfilled.

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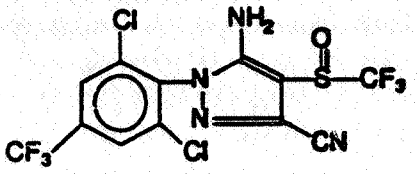
CHEMICAL STRUCTURE

M&B 46030 (Fipronil) belongs to the chemical class phenylpyrazoles and has the following chemical structure.



PROPOSED USE

The registrant is requesting an EUP/temporary tolerance for use of Fipronil 1.5% Granular to control wireworms and Northern and Western corn rootworm larvae. The proposed testing is for 130.0 lbs. of active ingredient to be applied on 1000 acres in 50 tests (in 8 states) at a maximum rate of 0.13 lbs. a.i./acre per application. The proposed temporary tolerances are as follows:

corn, field, grain - 0.02 ppm
corn, forage - 0.05 ppm
corn, fodder - 0.07 ppm

DATA SUMMARY

I. ACUTE TOXICITY TESTING WITH TECHNICAL M&B 46030

Acute Oral Toxicity/Rat (81-1): MRID # 429186-28

Material Tested: M&B 46030 (93% a.i.)

Acute oral LD_{50} (M) = 92 (64-128) mg/kg; LD_{50} (F) = 103 (73-141) mg/kg; LD_{50} (M+F) = 97 (76-122) mg/kg

Toxicity Category: II

Classification: Acceptable

Acute Dermal Toxicity/Rat (81-2): MRID # 429186-29

Material Tested: M&B 46030 (93% a.i.)

Acute dermal LD_{50} > 2000 mg/kg

Toxicity Category: III

Classification: Acceptable

Acute Dermal Toxicity/Rabbit (81-2): MRID # 429186-30

Material Tested: M&B 46030 (96.7% a.i.)

Acute dermal LD_{50} (M) = 445 (200-980) mg/kg; (F) = 354 (200-620) mg/kg; (M+F) = 354 (210-600) mg/kg

Toxicity Category: II

Classification: Acceptable

Acute Inhalation Toxicity/Rat (81-3): MRID # 429186-31

Material Tested: M&B 46030 (95.4% a.i.)

Dosage levels tested: 0.929, 0.523 and 0.259 mg/l
LC_{50} = 0.682 mg/l (males and females)

Toxicity Category: III

Classification: Supplementary

Primary Eye Irritation/ Rabbit (81-4): MRID # 429186-32

Material Tested: M&B 46030 (96.7% a.i.)

M&B 46030 produces mild, transient ocular irritation in rabbits.

Toxicity Category: III

Classification: Acceptable

Primary Dermal Irritation/Rabbit (81-5): MRID # 429186-33

Material Tested: M&B 46030 (96.7% a.i.)

M&B 46030 produces slight dermal irritation in rabbits.

Toxicity Category: IV

Classification: Acceptable

Dermal Sensitization/Guinea Pig (81-6): MRID # 429186-34

Material Tested: M&B 46030 (95.4% a.i.)

The chemical's ability to produce dermal sensitization could not be

determined with assurance due to study deficiencies.

Classification: Supplementary

II. ACUTE TOXICITY TESTING WITH METABOLITE

(All of the following studies were conducted with M&B 46136, 98% a.i.)

Acute Oral Toxicity/Rat (81-1): MRID # 429186-75

Acute oral LD_{50} (M) = 184 (104-312) mg/kg; LD_{50} (F) = 257 (158-490) mg/kg; LD_{50} (M+F) = 218 (97-670) mg/kg

Toxicity Category: II

Classification: Acceptable

Acute Dermal Toxicity/Rat (81-2): MRID # 429186-76

Acute dermal LD_{50} > 2000 mg/kg

Toxicity Category: III

Classification: Acceptable

Primary Eye Irritation/Rabbit (81-4): MRID # 429186-77

M&B 46136 produces slight ocular irrication in rabbits.

Toxicity Category: III

Classification: Acceptable

Primary Dermal Irritation/Rabbit (81-5): MRID # 429186-78

M&B 46136 is not a dermal irritant in rabbits.

Classification: Acceptable

III. ACUTE TOXICITY STUDIES WITH FORMULATION

(All the following studies were conducted with the formulation EXP 60655A, 1.6% a.i.)

Acute Oral Toxicity/Rat (81-1): MRID # 429186-36

Acute oral LD_{50} > 5000 mg/kg

Toxicity Category: IV

Classification: Acceptable

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Acute Dermal Toxicity/Rabbit (81-2): MRID # 429186-37

Acute dermal LD_{50} > 2000 mg/kg

Toxicity Category: III

Classification: Acceptable

Acute Inhalation Toxicity/Rat (81-3): MRID # 429186-38

Acute inhalation LC_{50} > 5.11 mg/l

Toxicity Category: IV

Classification: Acceptable

Primary Eye Irritation/Rabbit (81-4): MRID # 429186-39

EXP 60655A produces slight, transient ocular irritation in rabbits.

Toxicity Category: IV

Classification: Acceptable

Primary Dermal Irritation/Rabbit (81-5): MRID # 429186-40

EXP 60655A produces very slight dermal irritation in rabbits.

Toxicity Category: IV

Classification: Acceptable

Dermal Sensitization/Guinea Pig (81-6): MRID # 429186-41

The chemical's ability to produce dermal sensitization could not be determined with assurance due to study deficiencies.

Classification: Supplementary

DISCUSSION

Toxicology Branch II is in the process of reviewing the total toxicology data base for this chemical, including the chronic toxicity and carcinogenicity studies. Although this review is not complete, it is evident that there are concerns regarding carcinogenicity and neurotoxicity which prohibit a recommendation for a temporary tolerance for the chemical at this time. There is evidence of neurotoxicity in three species, the rat, mouse and dog at dosages as low as 1.5 ppm (0.059 and 0.078 mg/kg/day in the male and female, respectively) in the rat in the combined chronic toxicity/carcinogenicity study. There is also evidence that the chemical has a potent effect on thyroid function in rats and produces benign and malignant tumors in that gland at a dosage of

300 ppm (12.68 and 16.75 mg/kg/day in males and females, respectively). The review of the total data base will be completed shortly, and the chemical will be presented to the RfD/Peer Review Committee and the Cancer Peer Review Committee for evaluation.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/17/94
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: 429186-28
TEST MATERIAL:	M&B 46,030 Synonym: Fipronil
STUDY NUMBER:	881300D/M&B 290/AC
TESTING FACILITY:	Huntingdon Research Centre, Ltd. Cambridgeshire, England
SPONSOR:	Rhone-Poulenc, Ltd.
TITLE OF REPORT:	Acute Oral Toxicity to Rats of M&B 46,030
AUTHOR(S):	John Gardner
REPORT ISSUED:	October 17, 1988

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 429186-28), a single dose M&B 46,030 in corn oil was administered intragastrically to five male and five female CD rats per group at dosages of 50, 80, 126 or 200 mg/kg. The animals were observed for 14 days post-treatment for mortality. **The LD_{50} (95% confidence limits) was calculated as 92 (64 to 128) mg/kg for males, 103 (73 to 141) mg/kg for females and 97 (76 to 122) mg/kg for the combined sexes.**

The study is classified as **Acceptable** with a **TOXICITY CATEGORY II** and **satisfies** the guideline requirements (81-1) for an acute oral toxicity study in rats.

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I. MATERIALS

A. Test Material

Name: M&B 46,030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethylsulphinylpyrazole
Purity: 93%
Lot Number: IGB444
Description: Green solid
Storage Conditions: Ambient conditions of humidity and temperature in the dark

The chemical was prepared at various (w/v) concentrations in corn oil and administered at a volume of 10.0 ml/kg.

B. Test Animals

Species: CD [Crl:CD(SD) BR) rats
Source: Charles River U.K. Limited, England
Age: Four to six weeks
Weight: 100 to 138 g
Housing: Five rats/sex per wire mesh cage
Food and Water: Labsure LAD 1 and tap water *ad libitum*
Environmental Conditions: Temperature: 24 to 28°C
Relative humidity: 61%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour

Acclimation Period: 7 days

II. METHODS

In a preliminary experiment, groups of two males and two females were dosed at 25 or 100 mg/kg body weight. The acute oral LD_{50} in this study was approximately 100 mg/kg.

In the definitive study, male and female rats were administered the test substance via a syringe and plastic catheter as indicated below.

Dose (mg/kg)	Concentration (% w/v)	No. of Rats M	F
50	0.50	5	5
80	0.80	5	5
126	1.26	5	5
200	2.00	5	5

A 14-day observation period followed the treatment. Body weight was recorded on Day 1 (day of dosing), 8, 15 and at death. At the end

of the observation period, the surviving animals were sacrificed and necropsied. LD_{50} values were calculated by the method of: Finney (1971) Probit Analysis (3rd Edition) Cambridge University Press.

III. RESULTS

Death occurred at doses of 80 mg/kg and greater in males and females. The number of deaths per group is summarized below:

Dose Level (mg/kg)	Number of Deaths	
	Males	Females
50	0	0
80	2	2
126	4	4
200	5	4

Death occurred in the females within the first two days of the study and in the males within the first three days. The LD_{50} (95% confidence limits) was calculated as 97 mg/kg (76 - 122 mg/kg) for the combined sexes, 92 (64 to 128) mg/kg for males and 103 (73 to 141) mg/kg for females.

Clinical signs observed within five hours of dosing included piloerection, hunched posture, waddling gait and diarrhea. Lethargy was seen in animals treated at 80 mg/kg and above. Decreased respiratory rate, pallor of the extremities and/or ptosis were seen in a single male in the 80 mg/kg group and in all rats in the 200 mg/kg group. Clonic convulsions and prostration preceded death in two males and one female in the 200 mg/kg group. The clinical signs subsided by Day 3 in the 50 mg/kg group and by Day 6 for all the other dose levels.

Decreased body weight gain was recorded on Day 8 and beyond for two females at each dose level and for all surviving males. The only significant finding at necropsy was hydronephrosis in single male and female rats in the 80 mg/kg group. The finding is common in this strain of rat and was not considered to be treatment-related.

IV. COMPLIANCE

A statement was submitted by the sponsor indicating that the study was conducted in accordance with GLP regulations. A Statement of No Data Confidentiality Claim was submitted by the sponsor.

V. CONCLUSIONS

The LD_{50} (95% confidence limits) was calculated as 92 (64 to 128) mg/kg for males, 103 (73 to 141) mg/kg for females and 97 (76 to 122) mg/kg for the combined sexes.

The study is classified as **Acceptable** with a **TOXICITY CATEGORY II** and **satisfies** the guideline requirements (81-1) for an acute oral toxicity study in rats.

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 2/17/94
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: 429186-29
TEST MATERIAL:	M&B 46,030 Synonym: Fipronil
STUDY NUMBER:	881113D/M&B 291/AC
TESTING FACILITY:	Huntingdon Research Centre, Ltd Cambridgeshire, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	Acute Dermal Toxicity to Rats of M&B 46,030
AUTHOR(S):	John R. Gardner
REPORT ISSUED:	October 11, 1988

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 429186-29), a dose of 2 g/kg of technical M&B 46,030 was administered topically to five male and five female CD rats for 24 hours. There were no clinical signs of toxicity or mortalities. **The acute dermal LD_{50} for technical M&B 46,030 was greater than 2000 mg/kg.**

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) for a dermal toxicity (LD_{50}) study in rats.

I. MATERIALS

A. Test Material

Name: M&B 46,030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 93%
Batch Number: IGB444
Description: Green solid
Storage Conditions: Ambient temperature in the dark

The test material was prepared at a 90% w/v concentration in distilled water and administered at a volume of 2.2 ml/kg.

B. Test Animals

Species: CD rats
Source: Charles River U.K. Limited, Kent, England
Age: Seven to ten weeks prior to dosing
Weight: 201 to 250 g prior to dosing (Day 1)
Housing: Individually in metal cages
Food and Water: Labsure LAD 1 and tap water *ad libitum*
Environmental Conditions: Temperature: 23-28^0 C
Mean daily relative humidity: 61%
Photoperiod: 12 hours light/dark
Air changes: 15 per hour
Acclimation Period: Thirteen days

II. METHODS

One day before the test, an area approximately 50 x 50 mm (10% of total body surface) on the dorso-lumbar region of five male and five female rats was clipped. On the day of the exposure, 2 g/kg of M&B 46,030 was applied to the clipped area and covered with gauze and held in place with an impermeable dressing placed around the trunk. The dressing was removed after 24 hours and the skin was washed with warm water and blotted dry. The animals were observed frequently on Day 1 and twice daily for the remainder of the 14-day observation period. The treated skin was examined and assessed for dermal irritation twice daily. Body weights were measured on Days 1, 8 and 15. At the end of the observation period, the surviving animals were euthanized and subjected to gross necropsy examinations.

III. RESULTS

There were no clinical signs of toxicity or mortalities during the study. Body weight gain was slightly low for one male rat on Day 8 and for one female on Day 15. One female had a weight loss during

the first week of the observation period. The acute dermal LD_{50} for males and females was greater than 2 g/kg.

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 of No Data Confidentiality Claim by the sponsor.

V. CONCLUSIONS

The acute dermal LD_{50} for technical M&B 46,030 was greater than 2000 mg/kg.

The study is classified as Acceptable with a Toxicity Category III and satisfies the requirements (81-2) for a dermal toxicity (LD_{50}) study in rats.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/22/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 2/24/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity/Rabbits (81-2)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-30
TEST MATERIAL:	MB 46030 Synonym: Fipronil
STUDY NUMBER:	92N1009
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	MB 46030: Acute Percutaneous Toxicity Study in the Rabbit
AUTHOR(S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	December 8, 1992

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 429186-30), MB 46030 was applied to the entire trunk of groups of five male and five female New Zealand White rabbits at dosages of 0.10, 0.25, 0.50, 1.00 and 2.00 g/kg for 24 hours. All groups were observed for signs of mortality for 14 days post-treatment. The two lowest groups were observed for an additional 14 days due to delayed signs of toxicity and death in the highest dose groups. There was a variety of clinical signs observed; the severity was increased in the higher dose groups. Delayed convulsions were seen at all the dose levels except 0.10 g/kg. The majority of the lesions seen at necropsy involved the lungs and kidneys. **The acute dermal LD_{50} (95% confidence limits) was calculated as 445 (200 to 980) mg/kg for males, 354 (200 to 620) mg/kg for females and 354 (210 to 600) mg/kg for the combined sexes.**

The study is classified as **Acceptable** with a **Toxicity Category II** and **satisfies** the requirements (81-2) for a dermal toxicity study in rabbits.

I. MATERIALS

A. Test Material

Name: MB 46030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 96.7%
Batch Number: 78/GC/90
Description: White powder
Storage Conditions: Room temperature

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: 12 to 18 weeks
Weight: Males - 2.1 to 3.0 kg, Females - 2.3 to 2.9 kg at the time of dosing
Housing: Individually in cages with wire floors
Food and Water: AGWAY® PROLAB® Animal Diet High Fiber Rabbit and tap water *ad libitum*
Environmental Conditions: Temperature: 61-71° F
Relative Humidity: 40-60%
Photoperiod: 12 hours light/dark
Acclimation Period: At least one week

II. METHODS

At least one day before the application of the test chemical, the fur from the entire trunk of each rabbit was clipped. The next day, the test substance was moistened with corn oil and applied to the skin of five female and five male rabbits per group at dosages of 0.10, 0.25, 0.50, 1.00 or 2.00 g/kg body weight. A gauze sheeting was wrapped around the trunk and secured with tape and then covered with polyethylene sheeting. After 24 hours, the dressing was removed.

The treated animals were observed frequently on the day of dosing for clinical signs of toxicity and twice daily thereafter for 14 days. Due to delayed toxicity and delayed deaths in the highest dose groups, the observation period was extended to 28 days for the lowest groups (0.10 and 0.25 g/kg). Body weights were measured on the day of dosing and at 7 and 14 days after dosing or at death. Weights were also recorded at days 21 and 28 when applicable. After 14 or 28 days, the surviving animals were euthanized. Necropsies were performed after death or sacrifice. LD_{50} values were calculated by the moving average method (Thompson, 1947).

III. RESULTS

The amount of test chemical applied to each animal ranged from approximately 31 mg/cm^2 (at 0.10 g/kg) to 104 mg/cm^2 (at 2.00 g/kg). Deaths occurred at all except the lowest dose level. The number of deaths per group is presented below.

Males

Dose (g/kg)	Dead/Dosed	Days to Death
2.00	4/5	6,6,6,11
1.00	5/5	5,5,6,6,10
0.50	2/5	7,8
0.25	2/5	11,12
0.10	0/5	--

Females

Dose (g/kg)	Dead/Dosed	Days to Death
2.00	5/5	5,5,7,10,12
1.00	4/5	10,11,14,14
0.50	5/5	8,8,10,10,14
0.25	1/5	10
0.10	0/5	--

The acute dermal LD_{50} (95% confidence limits) was calculated as 0.445 (0.20 to 0.98) g/kg for males, 0.354 (0.20 to 0.62) g/kg for females and 0.354 (0.21 to 0.60) g/kg for the combined sexes.

There was no evidence of dermal irritation. Clinical signs of systemic toxicity included sluggishness, salivation, audible breathing, spasms, tremors, vocalization, hyperactivity, prostration, red discoloration on the perioral and perinasal fur, diarrhea and emaciation. Delayed convulsions which were initially observed at 3 to 9 days post-dosing were present at all dose levels except 0.1 g/kg. They were observed in both animals that died and survived. Mean body weights were increased in animals in the three lowest dose groups.

Necropsy of the animals that died revealed liquid in the thoracic cavity, discolored, patchy and/or mottled lungs and a moderate to large amount of blood in the urine. The following were observed at necropsy in the animals surviving until the end of the study: dark red lungs, red spots on the lungs, red lungs with gray areas, dark purple kidneys, blood in the kidneys, enlarged and pitted kidneys and an enlarged spleen.

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IV. COMPLIANCE

A statement was submitted by the sponsor indicating that the study meets the requirements of the Good Laboratory Practice regulations. A signed Quality Assurance statement was submitted by the testing facility. A statement claiming no data confidentiality was submitted by the sponsor.

V. CONCLUSIONS

The acute dermal LD_{50} (95% confidence limits) was calculated as 445 (200 to 980) mg/kg for males, 354 (200 to 620) mg/kg for females and 354 (210 to 600) mg/kg for the combined sexes.

The study is classified as **Acceptable** with a **Toxicity Category II** and satisfies the requirements (81-2) for a dermal toxicity study in rabbits.

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Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 2/17/94
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: 429186-31
TEST MATERIAL:	M&B 46,030 Synonym: Fipronil
STUDY NUMBER:	LSR 90/RHA358/0791
TESTING FACILITY:	Life Science Research Ltd. Suffolk, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	M&B 46030: Acute Inhalation Toxicity Study in the Rat
AUTHOR(S):	S. Cracknell
REPORT ISSUED:	January 10, 1991

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 429186-31), three groups of five male and five female CD albino rats were exposed to atmospheric concentrations of 0.929, 0.523 and 0.259 mg/l of M&B 46,030 for four hours. The animals were then observed for fourteen days for mortality and clinical signs of toxicity. At the end of the observation period, all surviving animals were sacrificed and necropsied. Clinical signs of toxicity observed during the post-exposure period included wet fur, brown staining, hypothermia, vocalization, tremors and hunched body posture. Mortality was observed at all the dose levels except in the low dose males. The lung weights of the animals which died before study termination were increased over the expected range. The percentage of particles in the test atmosphere less than 6 μm was 29.7, 45.0 and 40.0 for the 0.929, 0.523 and 0.259 mg/l groups, respectively. **The acute LC_{50} (95% confidence limits) was calculated as 0.682 mg/l for male and female rats combined.**

The study is classified as **Core Supplementary** with a **Toxicity Category III** and **does not satisfy** the requirements (81-3) of an acute inhalation toxicity (LC_{50}) in rats. The study may be upgraded if: 1) the mean mass aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the atmospheric particles are calculated; and 2) the registrant can demonstrate that efforts to produce smaller particles of test material were unsuccessful.

EX1025

I. MATERIALS

A. Test Material

Name: M&B 46030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 95.4%
Batch Number: PGS 963
Description: Fine, slightly yellow powder
Storage Conditions: Ambient temperature

B. Test Animals

Species: CD albino rats
Source: Charles River (U.K.) Limited, Kent, England
Age: 7 - 12 weeks at time of exposure
Weight: males - 243 to 283 g; females - 213 to 247 g
Environmental Conditions: Temperature: 18-25^0 C
Humidity: 40-70%
Photoperiod: 12 hours light/dark
Housing: Individually in polypropylene cages
Food and Water: LAD 1 and tap water *ad libitum* except during exposure
Acclimation Period: Six days

II. METHODS

Exposure Chamber

The aluminum alloy exposure chamber had a volume of approximately 60 liters and incorporated three animal exposure sections each having 20 exposure ports. The animals were exposed snout-only.

Atmosphere Generation and Monitoring

The powder canister of a Wright Dust Feed Mechanism was packed with the test chemical to a pressure of 100 kg/cm^2. The mechanism was positioned at the top of the exposure chamber. Atmospheric concentrations of the test chemical were varied by changing the gear ratio of the generator mechanism. Compressed air was passed through the mechanism at a flow rate of 25 l/min. The exhaust air was drawn from the base of the chamber and passed through an absolute filter before venting. A 5.5 minute equilibration time was allowed for the atmospheric concentration to reach 90% of the final value. (See the attached diagram of the exposure system, Figure 1 from the study report.)

The concentration of the chemical in the test atmosphere was determined gravimetrically on five occasions during the four-hour

exposure period. Samples were collected on a weighed Whatman GF/A glass fibre filter at a flow rate of approximately four liters per minute. The mass of M&B 46,030 in the atmosphere was calculated as difference in the weight of the filter pre- and post-exposure.

A Sierra Marple cascade impactor was used to determine the particle size distribution of the test atmosphere once during each hour of the exposure period. The fraction of the atmosphere considered to be inhalable to the laboratory rat, i.e. 6.0 µm or less, was calculated as the percentage of the total mass of the test material which was collected on stages three thru seven of the impactor.

The temperature and humidity within the chamber were monitored frequently and recorded at 30 minute intervals.

Animal Treatment

Three groups, each consisting of five male and five female rats, were exposed for four hours to M&B 46,030 nominal atmospheric concentrations of 2.134 (Group 1), 0.766 (Group 2) and 0.456 (Group 3) mg/l. The study report states that an additional range-finding study was performed using a single group of two male and two female rats exposed to a nominal concentration of 2.617 mg/l. The results of this trial indicated that the nominal concentration in the definitive study should be lower than this level.

The animals were observed for clinical signs of toxicity immediately before exposure, 15 and 30 minutes after exposure commenced and at 30 minute intervals for the remainder of the period. Post-exposure, they were observed at 30 minute intervals for the first three hours and subsequently were examined twice daily during the 14 day observation period. Gross necropsies were performed on animals which died. The animals were weighed daily both before and after the exposure period. At the end of the observation period, all the surviving animals were euthanized and subjected to gross necropsies. In addition, the lungs (with bronchi), liver and kidneys were weighed. These organs, along with the larynx, were also preserved in formaldehyde for possible histological examination.

The LC_{50} was calculated using the method of Finney (Finney, 1971).

III. RESULTS

Test Atmosphere

The nominal and achieved chamber concentrations of the test substance and the percentage of particles less than 6 µm for each group were as follows:

Group	Mean Achieved Concentration (mg/l)	Nominal Concentration (mg/l)	% Particles < 6 µm
1	0.929	2.134	29.7
2	0.523	0.766	45.0
3	0.259	0.456	40.0

Chamber temperatures were within the target range (22 ± 3° C) but the relative humidity was slightly higher than the target range (40-60%).

Test Animals

The mortality per group during the study is summarized below:

Group	Achieved concentrations M&B 46030 (mg/l)	Mortality Male	Female	Total
1	0.929	4/5	3/5	7/10
2	0.523	1/5	2/5	3/10
3	0.259	0/5	1/5	1/10

The LC_{50} (95% confidence limits) was calculated as 0.682 (0.426 - 0.938) mg/l.

All the deaths occurred during the first 48 hours post-exposure. Clinical signs observed during the exposure period included increased or decreased respiratory rate, struggling in the restraint tube and wet fur; these were considered non-specific responses to exposure to a particulate atmosphere. During the three hours immediately following the exposure, hypothermia was noted in all the Group 2 animals and in some Group 3. Signs also observed during this period included hunched posture, tremors and vocalizations when handled; brown staining of the fur and wet fur were seen in most animals. During Days 2 to 14 of the observation period, the following signs were recorded: piloerection, hunched posture, penis mutilation, yellow staining, salivation, tremors, convulsions, ataxia, hairloss and vocalizations when handled.

All the surviving animals initially lost weight post-exposure, however all the group mean body weights were increased over the course of the study.

Necropsy findings included incomplete collapse of the lungs, dark lungs, dark lymph nodes and dark liver. The study report states that these findings are common in control rats and their incidences were not considered to be of toxicological significance.

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According to the study report, the lung weights of the animals which died before the study termination were increased in five animals exposed at 0.929 mg/l, three at 0.523 mg/l and one at 0.259 mg/l. (There were no control animals in the study, therefore it is assumed that comparisons were made to historical control data although none was included in the study report.) The weights of the animals which survived were considered to be normal. Liver and kidney weights of both the animals which survived and those which died were normal.

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 claiming no data confidentiality.

V. DEFICIENCIES

1. The mean mass aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles in the test atmosphere should have been calculated.

2. The study report states that particles 6.0 μm or less is considered to be inhalable in the rat. The recommendation from the Technical Committee of the Inhalation Specialty Section, Society of Toxicology [Fundamental and Applied Toxicology 18, 321-327 (1992)] is that a size of 4 μm MMAD is an appropriate upper cutoff of particle size for acute inhalation toxicity testing. This requirement may be waived if the registrant can demonstrate that efforts to produce smaller particles of the test material were unsuccessful.

VI. CONCLUSIONS

The acute LC_{50} (95% confidence limits) was calculated as 0.682 mg/l for male and female rats combined.

The study is classified as **Core Supplementary** with a **Toxicity Category III** and **does not satisfy** the requirements (81-3) of an acute inhalation toxicity (LC_{50}) in rats. The study may be upgraded if: 1) the mean mass aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the atmospheric particles are calculated; and 2) the registrant can demonstrate that efforts to produce smaller particles of test material were unsuccessful.

Page 23 is not included in this copy.

Pages _____ through _____ 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.

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_____ 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.

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/17/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation/Rabbits (81-4)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-32
TEST MATERIAL:	MB 46030 Synonym: Fipronil
STUDY NUMBER:	93N1217B
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	MB 46030 (Technical): Ocular Irritancy Study in the Rabbit
AUTHOR (S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	April 30, 1993

EXECUTIVE SUMMARY: In an primary eye irritation study (MRID # 429186-32), a dose of 0.1 ml of MB 46030 was instilled into the lower eyelid of three male and three female New Zealand White rabbits. The eyes were examined at 1 hour and at 1, 2, 3, 7, 10 and 14 days following instillation and scored for signs of irritation. At 1 hour, five of six animals had positive scores for irritation involving the conjunctiva, cornea and iris. There were no positive scores at 24 hours. **The study demonstrated that MB 46030 produces mild, transient ocular irritation in rabbits.**

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

I. MATERIALS

A. Test Material

Name: MB 46030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 96.7%
Batch Number: 78/GC/90
Description: White powder
Storage Conditions: Room temperature

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: Approximately 12 to 18 weeks old
Weight: Males - 3.1 to 3.2 kg; Females - 2.4 to 2.5 kg at time of dosing
Housing: Individually in cages with wire floors
Food and Water: Agway® Prolab® Animal Diet High Fiber Rabbit and tap water *ad libitum*
Environmental Conditions: Temperature: 61-70° C
Humidity: 40-70%
Photoperiod: 12 hours light/dark
Acclimation Period: Five days

II. METHODS

Twenty-four hours prior to treatment, the eyes of six rabbits were examined using fluorescein stain and found to be normal. On the treatment day, 0.1 ml of MB 46030 was instilled into the conjunctival sac of one eye. The other eye served as an untreated control. The eyes were examined at 1 hour and at 1, 2, 3, 7, 10 and 14 days following instillation and scored for signs of irritation. A copy of the grading system used in the study is attached to the DER.

III. RESULTS

At one hour post-instillation, 5 of 6 animals had positive scores. The following signs of irritation were reported: iritis in 5/6 animals (score 1 on scale of 0-2); corneal opacity in 2/6 animals (score 1 on scale of 1-4); and conjunctival redness in 5/6 animals (score 2 on scale of 0-3). At 24 hours, there were no positive scores.

IV. COMPLIANCE

The following compliance documents were submitted: a signed

statement by the sponsor indicating that the study complies with the GLP Guidelines; a signed statement by the Quality Assurance Unit of the testing facility; and a signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that MB 46030 produces mild, transient ocular irritation in rabbits.

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

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_____ Identity of product inert ingredients.

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011025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I 2/17/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation/Rabbits (81-5)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-33
TEST MATERIAL:	MB 46030 Synonym: Fipronil
STUDY NUMBER:	93N1217A
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	MB 46030 (Technical): Cutaneous Irritancy in the Rabbit
AUTHOR (S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	April 30, 1993

EXECUTIVE SUMMARY: In an primary dermal irritation study (MRID # 429186-33), a dose of 0.5 g of MB 46030 moistened with 0.5 ml of corn oil was applied to the clipped skin of three male and three female New Zealand White rabbits for four hours. The skin was examined at 1 hour and at 1, 2, 3, and 7 days post-application and scored for signs of irritation. At 1 hour, all of the rabbits had very slight to well-defined erythema and three of six had very slight edema. At one day post-instillation, very slight erythema was noted in 4/6 rabbits; no edema was observed. On days 2 and 3, very slight erythema was reported in 1/6 animals. No signs of irritation were seen at day 7. The study demonstrated that MB 46030 produces slight dermal irritation in rabbits.

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

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I. MATERIALS

A. Test Material

Name: MB 46030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 96.7%
Batch Number: 78/GC/90
Description: White powder
Storage Conditions: Room temperature

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: Approximately 12 to 18 weeks old
Weight: Males - 3.1 to 3.4 kg; Females - 3.2 to 3.3 kg at time of dosing
Housing: Individually in cages with wire floors
Food and Water: Agway® Prolab® Animal Diet High Fiber Rabbit and tap water *ad libitum*
Environmental Conditions: Temperature: 61-71^0 C
Humidity: 40-70%
Photoperiod: 12 hours light/dark
Acclimation Period: Five days

II. METHODS

A few days before dosing, the dorsal area of the trunk of three male and three female rabbits was clipped. On the treatment day, 0.5 g of MB 46030 moistened with 0.5 ml of corn oil was applied to a 1-inch square patch which was secured to each rabbit with adhesive tape. A covering of polyethylene sheeting was then placed around the trunk and secured. The dressings were removed after four hours and the excess test substance was removed. The treated areas were examined for signs of dermal irritation and scored at 1 hour and at 1, 2, 3 and 7 days after the contact period. A copy of the grading system used in the study is attached to the DER. The animals were euthanized at the end of the 7-day observation period.

III. RESULTS

At one hour post-instillation, 5/6 animals had very slight erythema and 1/6 had well-defined erythema. Very slight edema was observed in 3/6 animals at that time. At one day post-instillation, very slight erythema was noted in 4/6 rabbits; no edema was observed. On days 2 and 3, very slight erythema was reported in 1/6 animals. No signs of irritation were seen at day 7.

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IV. COMPLIANCE

The following compliance documents were submitted: a signed statement by the sponsor indicating that the study complies with the GLP Guidelines; a signed statement by the Quality Assurance Unit of the testing facility; and a signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that MB 46030 produces slight dermal irritation in rabbits.

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

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____ Description of the product manufacturing process.

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____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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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 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 2/17/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Sensitization/Guinea Pigs (81-6)
EPA I.D. NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-34
TEST MATERIAL:	M&B 46030 Synonym: Fipronil
STUDY NUMBER:	LSR RHA/357
TESTING FACILITY:	Life Science Research Limited Suffolk, England
SPONSOR:	Rhone Poulenc Ag Company
TITLE OF REPORT:	M&B 46030: Dermal Sensitization Study in Guinea Pigs
AUTHOR(S):	K.D. Smith
REPORT ISSUED:	November 2, 1990

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID # 429186-34) using a modified Buehler method, ten male and ten female Dunkin-Hartley albino guinea pigs received three topical induction doses of 0.5 ml of 30% w/v M&B 46030 in paraffin oil for six hours at weekly intervals. A preliminary study using doses of 3% w/v to 30% w/v of the test material in paraffin oil demonstrated that the highest concentration was non-irritating. Challenge topical doses of 0.25 ml of either 30% w/v M&B 460300 in paraffin oil or 5% w/v M&B 46030 in paraffin oil were administered two weeks after the last induction application. The test sites were examined for signs of dermal irritation (erythema only) and scored at 24 and 48 hours after the challenge application. A score of 1 (faint erythema) or greater was considered to be a positive response. A control group of ten male and ten female guinea pigs were not treated during the induction phase but were treated at the challenge phase. On induction, there was no evidence of dermal irritation after any of the application sites. After the challenge application of 30% w/v M&B 46030, very faint erythema (±) was observed in one test and five control animals. After the challenge application of 5% w/v M&B 46030, very faint erythema (±) was observed in four test and five control animals.

A positive control chemical, dinitrochlorobenzene (DNCB) was tested using identical study procedures. A group of five male and five female guinea pigs were exposed to induction applications of 3% w/v DNCB in absolute ethanol and challenge applications of 0.1% w/v DNCB in acetone. A control group of five male and four female guinea pigs were exposed to challenge applications only. Signs of

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dermal irritation were observed in all the test animals during the induction phase. After the challenge applications, four of ten test animals had positive scores (1 or greater).

The chemical's ability to produce dermal sensitization could not be determined with assurance due to study deficiencies.

The study is classified as Core Supplementary due to: 1) concern that the induction dose was not high enough to test the sensitization potential of the chemical; and 2) the weak reactions in the positive control. The study **does not satisfy** the requirements (81-6) for a dermal sensitization study in guinea pigs. The study may be upgraded if the registrant submits: 1) data to demonstrate that the 30% induction dose was adequate; and 2) historical data with the positive control demonstrating that the reactions were as expected with this testing facility.

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I. MATERIALS

A. Test Material

Name: M&B 46030
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 95.4%
Lot Number: PGS963
Description: White powder
Storage Conditions: Ambient temperature protected from light

The test material was suspended in paraffin oil prior to dosing.

B. Test Animals

Species: Male and female albino guinea pigs, Dunkin-Hartley strain
Source: Olac Ltd., Oxfordshire, England
Age: Not provided
Weight: 321 - 449 g on Day 1
Housing: Five per sex in stainless steel cages
Food and water: Guinea-pig F.D.1. and tap water *ad libitum*[1]
Environmental Conditions: Temperature: 15-23°C
Relative Humidity: 40-70%
Photoperiod: 12 hours light/dark
Acclimation Period: Six days

II. METHODS

The study was conducted using a modified Buehler method.

Preliminary Test

In a preliminary test, four test sites on four guinea pigs were treated with 3%, 5%, 10% and 30% w/v M&B 46030 in paraffin oil for six hours. The study report states that the 30% w/v was considered the highest concentration practical for topical application. One animal had very faint erythema at the 5% site; no reaction was observed at the other sites. The criteria used for the selection of doses for the definitive study were that the concentration for induction should not cause severe irritation or necrosis of the test site and the concentration for the challenge should be the highest considered to be sub-irritant. Therefore, it was decided that the 30% concentration would be used for the induction dose and

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[1] On Day 22 of the study, the automatic watering system was inadvertently left closed off. The study report does not indicate how long the animals did not have access to water. It does state that all the animals showed weight loss but that the loss was rapidly recovered.

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both the 30% and 5% concentrations would be used for the challenge doses.

Induction Phase

Main Study Groups - Each treated (Group 2) and control (Group 1) group was composed of ten male and ten female guinea pigs. The control group was not treated during the induction phase but was exposed at the challenge phase.

Positive Control Groups - The treated group (Group 4) was composed of five males and five females; the control group (Group 3) contained five males and four females. (One female had a subcutaneous mass in the area of the right kidney and could not be replaced). The control group was only treated during the challenge phase.

One day prior to the application, an area approximately 5 cm x 5 cm on the left flank of each animal was clipped and shaved. On the day of treatment, a 2 x 2 cm patch soaked with 0.25 ml of 30% w/v M&B 46030 in paraffin oil was applied under occlusive bandages for six hours. The excess test material was washed from the site with paraffin oil when the bandages were removed. On the morning after the exposure, the test area was observed for signs of irritation. This procedure was repeated on days 8 and 15 during the induction phase of the study. The positive control group was treated in a like manner with 3% w/v Dinitrochlorobenzene (DNCB) in absolute ethanol.

Challenge Phase

On Day 28, an area approximately 5 cm x 5 cm on the right flank was clipped and shaved. The next day, two patches soaked with either 0.25 ml 30% w/v M&B 46030 in paraffin oil or 0.25 ml of 5% w/v M&B 46030 in paraffin oil were applied to the flank under occlusive bandages for six hours. The excess test material was washed off with paraffin oil when the bandages were removed. The positive control animals were treated in a like manner with 0.1% DNCB in acetone. The sites were depilated with a cream of calcium thioglycolate and washed to remove the residual cream approximately 22 hours after the challenge dose. The sites were observed and graded for a sensitization response 24 and 48 hours after the challenge application. The degree of reaction was scored for erythema only on the following scale:

Grade	Reaction to Treatment
0	No response
±	Very faint erythema, usually non-confluent
1	Faint erythema, usually confluent
2	Moderate confluent erythema
3	Severe confluent erythema

Only grades 1 and above were considered to be significant

erythematous reactions. Very faint erythema was considered to be a non-specific response to the dosing procedure. According to the study report, a test was considered positive when more than two of the twenty test group animals exhibit a significant erythematous reaction following challenge with a sub-irritant concentration of the test material.

Body weights were recorded at weekly intervals. At the end of the study, all the animals were euthanized with an intraperitoneal injection of a barbiturate.

Compliance

Signed statements of Quality Assurance and compliance with Good Laboratory Practice regulations were submitted by the testing facility. The sponsor submitted a statement claiming no data confidentiality.

III. RESULTS

None of the animals treated with M&B 46030 showed signs of dermal irritation during the induction phase. The study report does not indicate if any signs of dermal irritation were seen with the positive control during the induction phase. (The table on page 24 of Appendix 6 shows that by the third induction application, all of the treated animals had faint or moderate erythema.)

The challenge application of 30% M&B 46030 caused very faint erythema in one test and five control animals. The 5% concentration produced very faint erythema in four test and five control animals. The positive control application produced faint erythema in four test animals and very faint erythema in 4 test and 1 control animal.

All animals gained weight during the study.

IV. STUDY DEFICIENCIES

1. The registrant should demonstrate that the M&B 46030 dose was high enough to test the sensitization potential of the chemical. For induction, a dose should be chosen which produces mild to moderate irritation in preliminary irritation studies.[2] The study report states that 30% was the highest concentration considered practical for topical application, but does not give the basis for this conclusion.

2. The reactions of the positive control group after the challenge dose were rather weak. Only 3 of 5 males and 1 of 5 females had minimally positive scores (1 and above). The registrant should

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[2] Robinson MK, Nusair TL, Fletcher ER, Ritz HL. A review of the Buehler guinea pig skin sensitization test and its use in a risk assessment process for human skin sensitization. *Toxicology*. 1990; 61:91-107.

provide historical data using DNCB as a positive control to demonstrate that the weak reaction was acceptable for this testing facility.

IV. CONCLUSIONS

The chemical's ability to produce dermal sensitization could not be determined with assurance due to study deficiencies.

The study is classified as **Core Supplementary** due to: 1) concern that the induction dose was not high enough to test the sensitization potential of the chemical and 2) the weak reactions in the positive control. The study **does not satisfy** the requirements (81-6) for a dermal sensitization study in guinea pigs. The study may be upgraded if the registrant submits: 1) data to demonstrate that the 30% induction dose was adequate and 2) historical data with the positive control demonstrating that the reactions were as expected with this testing facility.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/15/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y M I 2/17/94
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: 429186-75
TEST MATERIAL:	M&B 46,136 Synonym: Fipronil
STUDY NUMBER:	881364D/M&B 286/AC
TESTING FACILITY:	Huntington Research Centre, Ltd. Cambridgeshire, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	Acute Oral Toxicity to Rats of M&B 46,136
AUTHOR(S):	John R. Gardner
REPORT ISSUED:	October 14, 1988

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 429186-75), groups of five male and five female CD rats were orally administered 10 ml/kg of M&B 46,136 in corn oil at dosages of either 64, 100, 160, 250, 400 or 640 mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. Clinical signs of toxicity were delayed until Day 2 in groups at 100 mg/kg and above and included hunched posture, abnormal gait, lethargy, pallor of the extremities, diarrhea, decreased respiratory rate, ataxia, increased salivation and clonic convulsions. **The acute oral LD_{50} (95% confidence limits) was calculated as 184 (104 to 312) mg/kg for males, 257 (158 to 490) mg/kg for females and 218 (97 to 670) mg/kg for the combined sexes.**

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

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I. MATERIALS

A. Test Material

Name: M&B 46,136
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 98%
Batch Number: WAB 212
Description: White solid
Storage Conditions: Ambient conditions in the dark

The test material was suspended at various concentrations (w/v) in corn oil for administration to the animals.

B. Test Animals

Species: CD rats [Crl:CD (SD) BR]
Source: Charles River U.K. Limited, Kent, England
Age: Four to six weeks old
Weight: 103 to 150 g on day of dosing
Housing: Up to five rats of same sex per cage
Environmental Conditions: Temperature: 25 -28^0 C
Relative Humidity: 61%
Photoperiod: 12 hours light/dark
Food and Water: Labsure LAD 1 and tap water *ad libitum*
Acclimation Period: One week

II. METHODS

In a trial test, groups of two male and two female rats were administered either 50 or 200 mg/kg. The LD_{50} in this trial was greater than 200 mg/kg.

In the definitive study, the following groups were treated with a single oral dose (10.0 ml/kg) using a syringe and plastic catheter.

Dose (mg/kg)	Concentration (% w/v)	Number of Rats Male	Female
64	0.64	5	5
100	1.00	5	5
160	1.60	10	10
250	2.50	10	10
400	4.00	5	5
640	6.40	5	5

The animals were observed frequently for mortality and clinical signs of toxicity on Day 1 (day of dosing) and twice daily for the

remainder of the 14-day observation period. Body weights were recorded on Days 1, 8 and 15 and at death. Surviving animals were sacrificed on Day 15. All animals were subjected to a gross necropsy.

The LD_{50} was calculated using the method of: Finney (1971) Probit Analysis (3rd Edition) Cambridge University Press.

III. RESULTS

Deaths occurred at doses of 100 mg/kg and above in both sexes. The number of deaths per group and the day of death are summarized below.

Sex	Dose (mg/kg)	Number of Deaths/ Number in Group	Day 1	Day 2	Day 3
Female	64	0/5	-	-	-
	100	2/5	-	2	-
	160	7/10	-	7	
	250	3/10	-	3	-
	400	4/5	-	4	
	640	5/5	-	3	2
Male	64	0/5	-	-	-
	100	2/5	-	2	-
	160	4/10	-	4	-
	250	4/10	-	3	1
	400	3/5	-	3	-
	640	4/5	-	4	-

The LD_{50} (95% confidence limits) was calculated as:

184 (104 to 312) mg/kg for males
257 (158 to 490) mg/kg for females
218 (97 to 670) mg/kg for the combined sexes

Clinical Signs

At 64 mg/kg, clinical signs seen within two hours of dosing included hunched posture and abnormal gait. At doses of 100 mg/kg and above, clinical signs (except for piloerection) were delayed until Day 2 and included hunched posture, abnormal gait, lethargy, pallor of the extremities, diarrhea, decreased respiratory rate, ataxia, increased salivation and clonic convulsions. Table 3 from

the study report listing the signs at each dose level is attached to the DER. Recovery in the surviving animals was completed by Day 5.

Body Weight

Low body weight was recorded on Day 8 for the majority of the male rats in the 100 mg/kg group and for up to three females at each dose level.

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 of No Confidentiality Claim by the sponsor.

V. CONCLUSIONS

The acute oral LD_{50} (95% confidence limits) was calculated as 184 (104 to 312) mg/kg for males, 257 (158 to 490) mg/kg for females and 218 (97 to 670) mg/kg for the combined sexes.

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

Page 42 is not included in this copy.

Pages _____ through _____ 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.

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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.

C11025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/1/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 2/12/94
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: 429186-76
TEST MATERIAL:	M&B 46,136 Synonym: Fipronil
STUDY NUMBER:	88961D/M&B 287/AC
TESTING FACILITY:	Huntington Research Centre, Ltd. Cambridgeshire, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	Acute Dermal Toxicity to Rats of M&B 46,136
AUTHOR(S):	John R. Gardner
REPORT ISSUED:	September 2, 1988

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 429186-76), a group of five male and five female CD rats were topically exposed to a single 2.0 g/kg dose of M&B 46,136 (88.2% w/v concentration in distilled water) for 24 hours. The animals were observed for mortality, clinical signs of toxicity and dermal irritation for 14 days post-dosing. There were no deaths, clinical signs of toxicity or evidence of dermal irritation. **The acute dermal LD_{50} was greater than 2 g/kg.**

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) of an acute dermal toxicity (LD_{50}) study in rats.

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I. MATERIALS

A. Test Material

Name: M&B 46,136
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 98%
Batch Number: WAB 212
Description: White solid
Storage Conditions: Ambient conditions in the dark

The test material was suspended at 88.2% w/v concentration in distilled water.

B. Test Animals

Species: CD rats [Crl:CD (SD) BR]
Source: Charles River U.K. Limited, Kent, England
Age: Seven to ten weeks
Weight: 204 to 249 g on day of dosing
Housing: Individually in metal cages
Environmental Conditions: Temperature: 24 -27^0 C
Relative Humidity: 59%
Photoperiod: 12 hours light/dark
Food and Water: Labsure LAD 1 and tap water *ad libitum*
Acclimation Period: Five days

II. METHODS

One day prior to treatment, the dorsolumbar region (approximately 10% of the total body surface) of five male and five female rats was clipped. On the day of treatment, M&B 46,136 was applied to an area approximately 50 x 50 mm at a dose of 2.0 g/kg (volume of 2.27 ml/kg). The area was then covered with gauze and held in place with an impermeable dressing around the trunk. After 24 hours, the dressings were removed and the treated areas were washed with warm water. The animals were observed for mortality and clinical signs of toxicity frequently on the day of dosing and twice daily for the remainder of the 14-day observation period. The treated areas were examined daily and scored for signs of dermal irritation. Body weights were recorded on Days 1, 8 and 15. All animals were sacrificed on Day 15 and subjected to gross necropsies.

III. RESULTS

There were no deaths nor clinical signs of toxicity. There were no signs of dermal irritation. Body weight gain was slightly lower than expected for four male and two female rats on Day 8 and for

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one male and one female rat on Day 15. There were no significant findings on 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 except that the purity of the test material was not adequately documented; 2) signed Quality Assurance statement by the testing facility; 3) Statement of No Confidentiality Claim by the sponsor.

V. CONCLUSIONS

The acute dermal LD_{50} was greater than 2 g/kg.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) of an acute dermal toxicity (LD_{50}) study in rats.

011025

Reviewed by: Virginia A. Dobozy, V.M.D.; M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I 2/17/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation (81-4)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-77
TEST MATERIAL:	M&B 46,136 Synonym: Fipronil
STUDY NUMBER:	881022D/M&B 289/SE
TESTING FACILITY:	Huntington Research Centre, Ltd. Cambridgeshire, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	Irritant Effects on the Rabbit Eye of M&B 46,136
AUTHOR(S):	Michael P. Liggett
REPORT ISSUED:	August 11, 1988

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID # 429186-77), a dose of 0.1 ml (60 mg) of M&B 46,136 was instilled into the lower eyelid of one eye of three male New Zealand White rabbits. The other eye served as an untreated control. The eyes were examined for signs of irritation and scored at 1 hour and 1, 2, 3, 4 and 7 days after instillation. One animal had a positive score for chemosis at one day post-instillation; no other positive scores were observed. **The study demonstrated that M&B 46,136 is a slight ocular irritant in rabbits.**

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

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I. MATERIALS

A. Test Material

Name: M&B 46,136
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 98%
Batch Number: WAB 212
Description: White solid
Storage Conditions: Ambient conditions in the dark

B. Test Animals

Species: New Zealand White rabbits
Source: Buckmasters, Hertfordshire, England and A. Smith, Surrey, England
Age: 11 to 14 weeks
Weight: 2.7 to 3.3 kg on day of dosing
Housing: Individually in metal cages
Environmental Conditions: Temperature: 19° C
Relative Humidity: 30-70%
Photoperiod: 12 hours light/dark
Food and Water: SDS Standard Rabbit Diet and tap water *ad libitum*
Acclimation Period: Not provided

II. METHODS

Prior to treatment, the eyes of three male rabbits were examined to ensure that there were no pre-existing lesions. A dose of 60 mg (volume of 0.1 ml) was then placed into the lower everted lid of one eye of each animal. The eyelid was then held closed for one second. The other eye served as an untreated control. The eyes were examined for signs of irritation and scored 1 hour and 1, 2, 3, 4 and 7 days after instillation. The grading system is attached to the DER.

III. RESULTS

A positive score for conjunctival chemosis was observed 1 day after instillation. Dulling of the cornea (not on the grading scale) was observed in one animal at 1 and 2 days post-instillation. Scores of 1 for conjunctival redness (not considered a positive score) were seen in all the rabbits until 4 days post-instillation.

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 except that the purity of the test material was not adequately documented; 2) signed Quality Assurance statement by the testing facility; 3) Statement of No Confidentiality Claim by the sponsor.

V. DEFICIENCY

Subdivision F of the Pesticide Assessment Guidelines require that six animals be used in the primary eye irritation study unless justification/reasoning for using fewer animals is provided. The registrant has not provided such justification/reasoning. However, only one of the three animals in the study had a positive score in one parameter at Day 1, the minimal change for assignment to Toxicity Category III. It is reasonable to assume that an additional three animals would not change this assignment.

VI. CONCLUSIONS

The study demonstrated that M&B 46,136 is a slight ocular irritant in rabbits.

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

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_____ Information about a pending registration action.

✓ FIFRA registration data.

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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.

011025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/16/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. JMI 2/17/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation (81-5)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-78
TEST MATERIAL:	M&B 46,136 Synonym: Fipronil
STUDY NUMBER:	88833D/M&B 288/SE
TESTING FACILITY:	Huntington Research Centre, Ltd. Cambridgeshire, England
SPONSOR:	Rhone-Poulenc Ltd.
TITLE OF REPORT:	Irritant Effects on Rabbit Skin of M&B 46,136
AUTHOR(S):	Michael P. Liggett
REPORT ISSUED:	July 27, 1988

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 429186-78), three male New Zealand White rabbits were topically exposed to a single 0.5 g/kg dose of M&B 46,136 (moistened with distilled water) for four hours. The treated areas were observed for signs of irritation (erythema and edema) on Days 1, 2, 3 and 4. There were no signs of dermal irritation in any of the rabbits. **The study demonstrated that M&B 46,136 is not a dermal irritant in rabbits.**

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

I. MATERIALS

A. Test Material

Name: M&B 46,136
Synonym: Fipronil
Chemical Name: 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethyl sulphonylpyrazole
Purity: 98%
Batch Number: WAB 212
Description: White solid
Storage Conditions: Ambient conditions in the dark

B. Test Animals

Species: New Zealand White rabbits
Source: A. Smith, Surrey, England
Age: 9 to 12 weeks
Weight: 2.1 to 2.7 kg on day of dosing
Housing: Individually in metal cages
Environmental Conditions: Temperature: 19^0 C
Relative Humidity: 30-70%
Photoperiod: 12 hours light/dark
Food and Water: SDS Standard Rabbit Diet and tap water *ad libitum*
Acclimation Period: Not provided

II. METHODS

One day prior to treatment, the dorso-lumbar region (approximately 10 cm square) of three male rabbits was clipped. On the day of treatment, 0.5 g of M&B 46,136 moistened with distilled water on a 2.5 cm square gauze pad was applied to the clipped area of each rabbit and covered with an elastic bandage. After four hours, the dressing was removed and the area was washed with water. The area was examined for signs of dermal irritation and scored on Day 1 (30 minutes after removal of the dressing) and on Days 2, 3, and 4.

III. RESULTS

There were no signs of dermal irritation at any of the observations.

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 except that the purity of the test material was not adequately documented; 2) signed Quality Assurance statement by the testing facility; 3) Statement of No

Confidentiality Claim by the sponsor.

V. DEFICIENCY

Subdivision F of the Pesticide Assessment Guidelines require that six animals be used in a primary dermal irritation study, unless justification/reasoning for using fewer animals is provided. The registrant did not provide such justification/reasoning for this study. However, there were no signs of dermal irritation in the rabbits tested in both this study and in the acute dermal toxicity study (MRID # 429186-76). Therefore, it is reasonable to assume that the addition of three more animals would not alter the findings of the study.

VI. CONCLUSIONS

The study demonstrated that M&B 46,136 is not a dermal irritant in rabbits.

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

011025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/22/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M.I. 2/22/94
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: 429186-36
TEST MATERIAL:	EXP 60655A Synonym: Fipronil
STUDY NUMBER:	92N1113A
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	EXP 60655A: Acute Peroral Toxicity Study in the Rat
AUTHOR(S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	March 8, 1993

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 429186-36), a group of five male and five female Sprague-Dawley rats were orally administered EXP 60655A as a 50% (w/v) suspension in distilled water at a dose of 5000 mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There were no deaths during the study. Clinical signs of toxicity included sluggishness, tremors followed by tonic convulsions (in 2 females), red crust on perinasal fur and single instances of aggressive behavior, kyphosis, hyperactivity and yellow staining of the perigenital fur. **The acute oral LD_{50} for EXP 60655A (1.6% fipronil) was greater than 5000 mg/kg.**

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: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethanesulphinylpyrazole
Purity: 1.6%
Reference Number: 46LEHX-92
Description: White to brown granules
Storage Conditions: Room temperature

For dosing, the test material was ground using an analytical mill and then was diluted with distilled water to prepare a 50% (w/v) suspension. The suspension was mixed on a magnetic stirrer prior to administration.

B. Test Animals

Species: Sprague Dawley albino rats
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN
Age: Males - 6 weeks; Females - 11 to 12 weeks when received
Weight: Males - 252 to 295 g; Females - 224 to 248 g when dosed
Housing: Up to five rats of same sex per stainless steel cage
Environmental Conditions: Temperature: 65-77^0 F
Relative Humidity: 40-70%
Photoperiod: 12 hours light/dark
Food and Water: Agway® Prolab® Animal Diet Rat, Mouse, Hamster 3000 and water *ad libitum*
Acclimation Period: Five days

II. METHODS

After an overnight fast, five male and five female rats were dosed with 5000 mg/kg EXP 60655A via stomach intubation using a stainless steel needle attached to a syringe. The dosing volume was adjusted to give 1 ml of dose per 100 g of body weight. The animals were observed frequently for mortality and clinical signs of toxicity on Day 1 (day of dosing) and twice daily for the remainder of the 14-day observation period. Body weights were recorded on the day of dosing and at 7 and 14 days post-dosing. At the end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

None of the animals died during the study. Clinical signs of toxicity were observed more frequently in the females. One male had sluggishness and red perinasal crust. Signs in the females included sluggishness, tremors followed by tonic convulsions (in 2), red

crust on perinasal fur and single instances of aggressive behavior, kyphosis, hyperactivity and yellow staining of the perigenital fur. Clinical signs were observed until 6 days post-dosing. All the animals gained weight over the course of the study. There were no lesions on gross necropsy. The acute oral LD_{50} was greater than 5000 mg/kg.

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) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute oral LD_{50} for EXP 60655A in rats (1.6% fipronil) was greater than 5000 mg/kg.

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.

011025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/22/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 2/22/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity/Rabbits (81-2)
EPA ID NUMBERS:	P. C. CODE: 129121 MRID NUMBER: 429186-37
TEST MATERIAL:	EXP 60655A Synonym: Fipronil
STUDY NUMBER:	92N1113B
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	EXP 60655A: Acute Percutaneous Toxicity Study in the Rabbit
AUTHOR(S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	March 8, 1993

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 429186-37), five male and five female New Zealand White rabbits were dermally administered EXP 60655A at a dose of 2 g/kg for 24 hours. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There were no deaths or clinical signs of toxicity during the study. Slight signs of dermal irritation were seen in one male and one female rabbit. **The acute dermal LD_{50} for EXP 60655A (1.6% fipronil) was greater than 2 g/kg.**

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rabbits.

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I. MATERIALS

A. Test Material

Name: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethanesulphinylpyrazole
Purity: 1.6%
Reference Number: 46LEHX-92
Description: White to brown granules
Storage Conditions: Room temperature

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: 12 to 18 weeks
Weight: Males - 2.4 to 3.0 kg; Females - 2.7 to 2.8 kg at dosing
Housing: Individually in cages
Environmental Conditions: Temperature: 61-71^0 F
Relative Humidity: 40-60%
Photoperiod: 12 hours light/dark
Food and Water: Agway® Prolab® Animal Diet High Fiber Rabbit and water *ad libitum*
Acclimation Period: Five days

II. METHODS

At least one day prior to dosing, the entire trunk of five male and five female rabbits was clipped. On the day of dosing, a dose of 2 g/kg of EXP 60655A moistened with corn oil was spread over as large a skin area as possible. The treated area was then wrapped with gauze and polyethylene sheeting for 24 hours. The animals were observed frequently for mortality and clinical signs of toxicity on Day 1 (day of dosing) and twice daily for the remainder of the 14-day observation period. Body weights were recorded on the day of dosing and at 7 and 14 days post-dosing. At the end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

The amount of test substance/area covered ranged from approximately 82 mg/cm^2 (for males) to 87 cm^2 (for females). None of the animals died nor were there any clinical signs of toxicity during the study. There were slight dermal reactions (erythema and desquamation) in one male and one female. All animals gained weight during the study and there were no lesions on gross necropsy. The acute dermal LD_{50} was greater than 2 g/kg.

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) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute dermal LD_{50} for EXP 60655A (1.6% fipronil) in rabbits was greater than 2 g/kg.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rabbits.

C11025

Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/22/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I 2/22/94
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: 429186-38
TEST MATERIAL:	EXP 60655A Synonym: Fipronil
STUDY NUMBER:	92N1060
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	EXP 60655A: Acute Dust Inhalation Toxicity Study in Rats
AUTHOR(S):	D. J. Nachreiner
REPORT ISSUED:	January 29, 1993

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 429186-38), five male and five female Sprague Dawley rats were exposed to an atmospheric concentration of 5.11 mg/l of EXP 60655A for four hours. The concentration of the test material in the atmosphere was determined gravimetrically seven times during the exposure. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were determined twice during the exposure. The nominal concentration of the test material was calculated by dividing the weight of the chemical delivered by the volume of air which passed through the chamber during the exposure period. 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 or observation period. The only clinical signs observed were during and immediately after the exposure and included blepharospasm, perinasal wetness and brown discoloration of the fur in both sexes. The nominal concentration of the test material was 37.4 mg/l. The mean gravimetric concentration was 5.11 (± 0.34) mg/l. The mean MMAD was 2.682 μ with a GSD of 1.636. **The acute inhalation LC_{50} for EXP 60655A (1.6% fipronil) was greater than 5.11 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.

I. MATERIALS

A. Test Material

Name: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 1.6%
Reference Number: 46LEHX-101
Description: Tan powder
Storage Conditions: Ambient temperature

The test substance was air milled before it was received at the testing facility.

B. Test Animals

Species: Sprague Dawley rats
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN
Age: 55 days at time of exposure
Weight: males - 246 to 286 g; females - 174 to 186 g at day of exposure
Environmental Conditions: Temperature: 64-79^0 F
Humidity: 40-70%
Photoperiod: 12 hours light/dark
Housing: Five per cages except during exposure when housed individually
Food and Water: Agway® Prolab® Animal Diet Rat, Mouse, Hamster 3000 *ad libitum* except during exposure
Acclimation Period: Five days

II. METHODS

Exposure Chamber

The plexiglas and stainless steel exposure chamber had a volume of approximately 120 liters. Air flow through the chamber was 29.5 l/min. The theoretical time required for the chamber to reach 99% of the target concentration was 18.7 min.

Atmosphere Generation and Monitoring

The test atmosphere was generated using a stainless steel auger-type dust feed - a feeder with a ½-inch diameter auger and an 11 rpm motor operated at 42.5 to 50%. A diagram of the test system is attached to the DER. The test material was placed into a hopper where it was constantly agitated. There was a hole in the base of the hopper where the test material was transported by an auger to the end of a tube. There, the dust was carried by a venturi-generated air stream to the chamber inlet where a baffle with a countercurrent airflow dispersed the dust throughout the chamber. The air was removed from the chamber via a vacuum line to two glass jars containing approximately two liters of water and a charcoal

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filter.

The concentration of the chemical in the test atmosphere was determined gravimetrically on seven occasions during the four-hour exposure period. Samples were collected for five minutes on a glass fiber filter at a flow rate of approximately 4.4 l/min.

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 TSI Aerodynamic Particle Sizer Model APS 3300 was used to determine the particle size distribution of the test atmosphere twice during the exposure period. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were calculated.

The temperature and humidity within the chamber were monitored; the frequency was not stated in the study report.

Animal Treatment

Five male and five female rats were administered a four-hour whole-body exposure at a target concentration of 5.0 mg/l (limit dose). 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 at 7 and 14 days following the exposure. At the end of the study, all the surviving animals were sacrificed and necropsied.

III. RESULTS

Test Atmosphere

The nominal concentration of the test material was 37.4 mg/l. The mean gravimetric concentration based on seven samples was 5.11 (± 0.34) mg/l. The mean MMAD was 2.682 μ with a GSD of 1.636.

The mean chamber temperature and relative humidity were 24^0 C and 47%, respectively.

No animals died during the exposure or observation period. The only clinical signs observed during and immediately after the exposure for both sexes were blepharospasm, perinasal wetness and brown discoloration of the fur. The animals appeared normal during the observation period.

All the animals gained weight over the course of the study. On necropsy, one male and one female each had discoloration of the thymic region and lungs which were considered to be incidental findings.

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 claiming no data confidentiality.

V. CONCLUSIONS

The acute inhalation LC_{50} for EXP 60655A (1.6% fipronil) was greater than 5.11 mg/l. The mean MMAD was 2.682 μ with a GSD of 1.636.

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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_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

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_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 2/22/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 2/22/94
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: 429186-39
TEST MATERIAL:	EXP 60655A Synonym: Fipronil
STUDY NUMBER:	92N1113D
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	EXP 60655A: Primary Eye Irritancy Study in the Rabbit
AUTHOR(S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	March 8, 1993

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID # 429186-39), 0.1 ml (80 mg) of EXP 60655A was instilled into the conjunctival sac of one eye of three male and three female New Zealand White rabbits. The other eye served as an untreated control. The eyes were examined for signs of irritation and scored at 1, 24, 48 and 72 hours and at 7 days post-dosing. The only positive score (according to the Draize grading scale) was for iritis in one female at one hour post-dosing. **The study demonstrated that EXP 60655A (1.6% fipronil) produces slight, transient ocular irritation in rabbits.**

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

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I. MATERIALS

A. Test Material

Name: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethanesulphinylpyrazole
Purity: 1.6%
Reference Number: 46LEHX-92
Description: White to brown granules
Storage Conditions: Room temperature

The test material was ground with a mortar and pestle to form a suitable powder for dosing.

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: 12 to 18 weeks
Weight: Males - 2.7 to 3.2 kg; Females - 2.9 to 3.1 kg at dosing
Housing: Individually in cages
Environmental Conditions: Temperature: 61-70^0 F
Relative Humidity: 40-70%
Photoperiod: 12 hours light/dark
Food and Water: Agway® Prolab® Animal Diet High Fiber Rabbit and water *ad libitum*
Acclimation Period: Five days

II. METHODS

Within 24 hours of dosing, the eyes of three male and three female rabbits were examined using fluorescein stain. A dose weight (80 mg) equivalent to a volume of 0.1 ml of EXP 60655A was then instilled into the conjunctival sac of one eye of each animal. The other eye served as an untreated control. The eyes were examined for evidence of irritation and scored at 1, 24, 48 and 72 hours and at 7 days post-dosing. A copy of the grading scale is attached to the DER. Fluorescein staining was used for the examinations beginning on day 1. The animals were sacrificed at Day 7.

III. RESULTS

The only positive score was for iritis at one hour post-dosing in one female. Slight conjunctival redness and discharge were observed at 1 and 24 hours post-instillation, however the scores were not considered positive. All of the eyes were clear at 48 hours, but slight conjunctival redness (not a positive score) was observed in one animal at 72 hours. The study demonstrated that EXP 60655A

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produced slight, transient ocular irritation in rabbits.

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) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that EXP 60655A (1.6% fipronil) produces slight, transient ocular irritation in rabbits.

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

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Pages _____ through _____ 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.

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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 2/22/94
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: 429186-40
TEST MATERIAL:	EXP 60655A Synonym: Fipronil
STUDY NUMBER:	92N1113C
TESTING FACILITY:	Bushy Run Research Center Export, PA
SPONSOR:	Rhone-Poulenc Ag Company
TITLE OF REPORT:	EXP 60655A: Primary Skin Irritancy Study in the Rabbit
AUTHOR(S):	R.C. Myers and S.M. Christopher
REPORT ISSUED:	March 8, 1993

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 429186-40), 0.5 g of EXP 60655A moistened with 0.5 ml of corn oil was topically applied to a clipped skin area of three male and three female New Zealand White rabbits for four hours. The treated areas were examined for signs of dermal irritation (edema and erythema) and scored at 1, 24, 48 and 72 hours and at 7 days post-treatment. Very slight erythema was observed in one female at 24, 48 and 72 hours. This animal also had desquamation of the treated area at 7 days post-treatment. **The study demonstrated that EXP 60655A (1.6% fipronil) produces very slight dermal irritation in rabbits.**

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

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I. MATERIALS

A. Test Material

Name: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethanesulphinylpyrazole
Purity: 1.6%
Reference Number: 46LEHX-92
Description: White to brown granules
Storage Conditions: Room temperature

B. Test Animals

Species: New Zealand White rabbits
Source: Hazleton Research Products, Inc., Denver, PA
Age: 12 to 18 weeks
Weight: Males - 2.5 to 2.9 kg; Females - 3.2 to 3.4 kg at dosing
Housing: Individually in cages
Environmental Conditions: Temperature: 61-71^0 F
Relative Humidity: 40-60%
Photoperiod: 12 hours light/dark
Food and Water: Agway® Prolab® Animal Diet High Fiber Rabbit and water *ad libitum*
Acclimation Period: Five days

II. METHODS

Within a few days of dosing, the dorsal area of the trunk of three male and three female rabbits was clipped. On the day of dosing, 0.5 g of EXP 60655A moistened with 0.5 ml of corn oil on a gauze patch was applied to the skin and then covered with polyethylene sheeting. The animals were placed into restraining devices for the four hour exposure period. At the end of the exposure, the bandages were removed and the excess test material was cleared from the treated sites. The areas were examined for signs of dermal irritation and scored at 1, 24, 48 and 72 hours and at 7 days post-dosing. A copy of the grading scale is attached to the DER. All rabbits were sacrificed at Day 7.

III. RESULTS

Very slight erythema was observed in one female at 24, 48 and 72 hours. This animal also had desquamation of the treated area at 7 days post-treatment. Edema of the application sites was not observed in any of the animals. The study demonstrated that EXP 60655A produces very slight dermal irritation in rabbits.

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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) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that EXP 60655A (1.6% fipronil) produces very slight dermal irritation in rabbits.

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

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_____ 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.

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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 2/22/94
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization/Guinea Pigs (81-6)

EPA I.D. NUMBERS: P. C. CODE: 129121
MRID NUMBER: 429186-41

TEST MATERIAL: EXP 60655A
Synonym: Fipronil

STUDY NUMBER: 92N1135

TESTING FACILITY: Bushy Run Research Center
Export, PA

SPONSOR: Rhone Poulenc Ag Company

TITLE OF REPORT: EXP 60655A: Dermal Sensitization Study in the Guinea Pig Using the Buehler Technique

AUTHOR(S): R.C. Myers and S.M. Christopher

REPORT ISSUED: March 15, 1993

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID # 429186-41) using a modified Buehler method, five male and five female Hartley albino guinea pigs received three topical induction doses of 0.3 ml of 40% (w/v) EXP 60655A in 0.25% (w/v) methyl cellulose for six hours at weekly intervals. A preliminary study using doses of 25% w/v and 40% (w/v) of the test material in 0.25 % (w/v) methyl cellulose demonstrated that the highest concentration was non-irritating. A challenge topical dose of 0.3 ml of 40% (w/v) EXP 60655A in 0.25% (w/v) methyl cellulose was administered two weeks following the last induction dose. The test sites were examined for signs of dermal irritation (erythema only) and scored at 24 and 48 hours after both the induction and challenge applications. A score of 1 (slight, solid erythema or moderate patchy erythema) or greater was considered to be a positive response. A control group of five male and five female guinea pigs was not treated during the induction phase but were treated at the challenge phase. On induction and challenge with the test material, there was no evidence of dermal irritation at any of the application sites in the test animals. The control animals were negative after the challenge application.

A positive control chemical, 2,4-dinitro-1-chlorobenzene (DNCB) was tested using identical study procedures. A group of five male and five female guinea pigs were exposed to induction applications of 0.3% (w/v) DNCB in 0.25% (w/v) methyl cellulose and challenge applications of 0.1% (w/v) DNCB in 0.25% (w/v) methyl cellulose. A control group of five male and four female guinea pigs was exposed to challenge applications only. Positive signs of dermal irritation

were observed in all the test animals after the second induction dose. After the challenge application, all ten test animals had slight solid to severe erythema at 24 and 48 hours. The control animals were negative after the challenge application.

The chemical's ability to produce dermal sensitization in guinea pigs could not be determined with assurance due to the study deficiency.

The study is classified as **Core Supplementary** due to concern that the induction dose was not high enough to test the sensitization potential of the chemical. The study does not satisfy the requirements (81-6) for a dermal sensitization study in guinea pigs. The study may be upgraded if the registrant submits data to demonstrate that the 40% induction dose was adequate.

I. MATERIALS

A. Test Material

Name: EXP 60655A
Synonym: Fipronil
Chemical Name: 5-amino-1-(2,6-dichloro-4-trifluoromethyl phenyl)-3-cyano-4-trifluoromethyl sulphinylpyrazole
Purity: 1.6%
Lot Number: 46LEHX-92
Description: White to brown granules
Storage Conditions: Room temperature

The test material was suspended in the appropriate amount of 0.25% (w/v) aqueous methyl cellulose solution for dosing. For the preliminary trials, concentrations of 25 or 40% (w/v) of EXP 60655A were used. At concentrations higher than 50% (w/v), a homogeneous suspension was not formed. The positive control, 2,4-dinitro-1-chlorobenzene (DNCB), was also suspended in 0.25% (w/v) aqueous methyl cellulose.

B. Test Animals

Species: Male and female albino guinea pigs, Hartley strain
Source: Hazleton Research Products, Denver, PA
Age: Males - 28 days; Females - 38 days when received
Weight: Males - 422 to 483 g; Females - 432 to 502 g at dosing
Housing: Individually in stainless steel cages
Food and water: Agway® Prolab® Animal Diet Guinea Pig and tap water *ad libitum*
Environmental Conditions: Temperature: 70-74^{0}F
Relative Humidity: 47-61%
Photoperiod: 12 hours light/dark
Acclimation Period: 38 days

II. METHODS

The study was conducted using a modified Buehler method.

Preliminary Test

In a preliminary test, the primary irritancy potentials of EXP 60655A and the positive control, DNCB, were tested at two sites on three animals per chemical. On the day prior to application, the application sites were clipped. On the day of dosing, the animals were placed in a "Newman" stainless steel restrainer and a volume of 0.3 ml of either the test or control chemical in a Hill Top Chamber® was applied. The area was then covered for six hours with an adhesive patch and then rubber dental dam was wrapped over the animal's dorsal surface. At the end of the exposure period, the animals were removed from the restrainer and the application sites were rinsed with warm water. At 1 day after the application, each site was clipped and depilated using Neet® Lotion Hair Remover. The treated areas were evaluated and scored for signs of erythema at 24

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and 48 hours using the following scale.

Grade	Reaction to Treatment
0	No reaction
0+	Slight patch erythema
1	Slight, solid erythema or moderate patchy erythema
2	Moderate erythema
3	Severe erythema (with or without edema)

In the preliminary trial, 25 and 40% (w/v) suspensions of EXP 60655A and 0.1 and 0.3% (w/v) suspensions of DNCB were tested. There was no evidence of dermal irritation with either the 25 or 40% suspensions at 24 or 48 hours, therefore the 40% suspension was selected for both the induction and challenge doses in the definitive study. The 0.3% DNCB produced minimal irritation (slight patchy erythema) on all three animals at 24 and 48 hours. The 0.1% suspension caused slight patchy erythema on 1 of 3 animals at 24 and 48 hours. Therefore, the 0.3% suspension was selected for the induction dose and the 0.1% suspension for the challenge application in the definitive study.

Induction Phase

The animals were assigned to four groups as summarized below.

Group	Number of Animals Male	Female	Induction Dose Concentration	Challenge Dose Concentration
EXP 60655A (Treated)	5	5	40%	40%
EXP 60655A (Control)	5	5	-	40%
DNCB (Treated)	5	5	0.3%	0.1%
DNCB (Control)	5	5	-	0.1%

A total of three weekly induction doses were applied using the procedure described in the preliminary test. For the test material, all three induction applications were made to the left scapular area. The positive control was applied at different locations between the left scapular and lumbosacral areas because irritation and staining were present after each induction dose. Evaluations for signs of dermal irritation were made at 24 and 48 hours post application.

Challenge Phase

Two weeks following the last induction dose, the challenge doses of the test and control chemicals were applied to the right scapular region of both the treated and control animals using the same

procedure as in the induction phase. The application sites were examined at 24 and 48 hours post-dosing.

At the end of the study, all the animals were euthanized with a CO_2 overdose.

Compliance

Signed statements of Quality Assurance and compliance with Good Laboratory Practice regulations were submitted by the testing facility. The sponsor submitted a statement claiming no data confidentiality.

III. RESULTS

The 40% (w/v) EXP 60655A did not produce signs of dermal irritation in the treated animals after any of the three induction doses. No signs of irritation were seen in the treated or control animals after the challenge dose of 40% (w/v) EXP 60655A.

Slight to moderate erythema (scores of 1 to 2) was observed in all of the animals treated with 0.3% (w/v) DNCB following the second and third induction doses. A grade of 1 or more was considered positive because no reactions on the control animals were greater than 0+ (0.5). Five animals also had edema at 24 and/or 48 hours following the third dose. The challenge dose of 0.1% (w/v) DNCB produced slight to severe erythema (scores of 1 to 3) in all the treated animals. No evidence of skin irritation was seen in the control animals.

IV. STUDY DEFICIENCY

The registrant should demonstrate that the EXP 60655A induction dose was high enough to test the sensitization potential of the chemical. For induction, a dose should be chosen which produces mild to moderate irritation in preliminary irritation studies.[1] The study report (page 8) states that for preliminary testing, the test substance was dosed at either 25% or 40% (w/v) suspensions because it did not form a homogeneous suspension at a higher concentration (50%). However, it is unclear if homogeneous suspensions could be formed at higher concentrations with other vehicles.

IV. CONCLUSIONS

The chemical's ability to produce dermal sensitization could not be determined with assurance due to the study deficiency.

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[1] Robinson MK, Nusair TL, Fletcher ER, Ritz HL. A review of the Buehler guinea pig skin sensitization test and its use in a risk assessment process for human skin sensitization. *Toxicology*. 1990; 61:91-107.

The study is classified as **Core Supplementary** due to concern that the induction dose was not high enough to test the sensitization potential of the chemical. The study **does not satisfy** the requirements (81-6) for a dermal sensitization study in guinea pigs. The study may be upgraded if the registrant submits data to demonstrate that the 40% induction dose was adequate.