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

DEC 20 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Fipronil - Review of Registrant's Response to Upgrade Acute Inhalation and Dermal Sensitization Studies

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FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer Virginia A Dobozy 12.9.94
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Health Effects Division (7509C)

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

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y.M. Ioannou 12/19/94
Review Section I, Toxicology Branch II
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and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) M. van Gemert 12/20/94

Registrant: Rhone-Poulenc Ag Company

Action Requested: Review registrant's response to upgrade acute inhalation and dermal sensitization studies

Recommendation: Toxicology Branch II has reviewed the registrant's response. The acute inhalation study with the technical chemical should be repeated using milled material. The dermal sensitization studies with the technical and formulated material are upgraded to acceptable. The Magnusson-Kligman Maximization Test with the technical material referred to in the registrant's response should be submitted.

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BACKGROUND

In a memo dated June 7, 1994 from Virginia Dobozy to Robert Brennis/Daphne Waldo/PM 10, Toxicology Branch II made the following recommendations for upgrading the studies in question.

MRID # 429186-31 - Acute Inhalation Study with Technical Fipronil - 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.

MRID # 429186-34 - Dermal Sensitization with Technical Fipronil - 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.

MRID # 429186-41 - Dermal Sensitization with 1.6% Formulation - The study may be upgraded if the registrant submits data to demonstrate that the 40% induction was adequate.

REGISTRANT'S RESPONSE

MRID # 429186-31 - Acute Inhalation Study with Technical Fipronil

The MMAD (designated as MMEAD, mass median equivalent aerodynamic diameter in England) was calculated as follows:

Group	Mean Achieved Concentration M&B 46030 (mg/l ± SD)	MMEAD (µm) ± SD
1	0.929 ± 0.05	8.5 ± 2.6
2	0.523 ± 0.04	6.4 ± 3.2
3	0.259 ± 0.03	6.8 ± 2.3

The test material was not milled to reduce particle size. The registrant argues that the appropriate acute toxicity category can be assigned based on the current study even though the particle size does not meet EPA's requirement of 4 µm MMAD. "With an MMAD of 4 µm, 50% of the particles would be less than this size. Based on the particle size distribution provided in the report, approximately 20% of the particles were less than 3.5 µm. Thus, approximately 40% of the 50% target less than 4 µm was achieved. Using this information, an LC50 value of 0.27 mg/L for particles in the required range can be extrapolated from the LC50 value of 0.68 mg/L determined in the study (i.e. 0.4 x 0.68 = 0.27). This value of 0.27 mg/L places fipronil technical in Toxicity Category II using either the criteria in the 1993 Code of Federal Regulations (40 CFR 156.01) or the proposed criteria issued in the Federal Register in 1984 (FR Vol 49, No. 188, pages 37981 to 37983)."

MRID # 429186-34 - Dermal Sensitization Study with Technical Fipronil

The registrant responded that a formulation trial was undertaken before commencement of treatment with 50%, 30% and 10% w/v formulations of M&B 46030 in paraffin oil. There was insufficient vehicle at the 50% concentration to adequately mobilize the test material. Therefore, the 30% concentration was considered to be the highest practical concentration for dermal application.

Regarding the relatively mild response to the positive control, DNCB, the registrant responded that two other positive control tests were undertaken in 1990, using the same vehicles and the same concentrations of DNCB. The results of those studies (from Pharmaco LSR) submitted with the response show similar reactions with DNCB as the study in question.

Accepting the registrant's response concerning these two issues, the technical chemical would be considered a non-sensitizer. (Only very faint erythema, graded ±, was observed with 30% and 5% challenge doses of M&B 46030 with greater than 1 considered positive.) However, in Attachment B of the registrant's response on page 4, there is a reference to results of a Magnusson-Kligman Maximization test with technical fipronil which suggests that the chemical is possibly a mild sensitizer. This study has not been reviewed by Toxicology Branch II.

MRID # 429186-41 - Dermal Sensitization with 1.6% Formulation

The registrant responded that concentrations of 50% and higher did not produce a homogeneous suspension in the aqueous methylcellulose and thus could not be dosed. The use of other vehicles such as acetone or ethanol is generally not practical because the solvents tend to dry the skin. As the formulated product is more than [redacted] it is dispersable but not soluble in any vehicle.

CONCLUSIONS

MRID # 429186-31 - Acute Inhalation Study with Technical Fipronil

Toxicology Branch II does not agree with the registrant's extrapolation and calculation of a LC_{50} value of 0.27 mg/L. The study should be repeated using milled technical chemical to achieve a MMAD of less than 4 µm.

MRID # 429186-34 - Dermal Sensitization Study with Technical Fipronil

Toxicology Branch II agrees with the registrant's response and the study is upgraded to acceptable. Based on this study, the technical chemical did not produce dermal sensitization. A revised EXECUTIVE

SUMMARY is attached. The registrant should submit the Magnusson-Kligman Maximization test with technical fipronil referred to in this submission.

MRID # 429186-41 - Dermal Sensitization with 1.6% Formulation

Toxicology Branch II agrees with the registrant's response and the study is upgraded to acceptable. Based on this study, the formulation did not produce dermal sensitization. A revised EXECUTIVE SUMMARY is attached.

MRID 429186-34 - "M&B 46030: Dermal Sensitization Study in Guinea Pigs"

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 0.25 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 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).

Technical M&B 46030 did not produce evidence of dermal sensitization in this study.

The study is classified as **Acceptable** and satisfies the requirements (81-6) for a dermal sensitization study in guinea pigs.

MRID # 429186-41 - "EXP 60655A: Dermal Sensitization Study in the Guinea Pig Using the Buehler Technique"

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 fipronil formulation (1.6% a.i.) did not produce evidence of dermal sensitization in this study.

The study is classified as **Acceptable** and **satisfies** the requirements (81-6) for a dermal sensitization study in guinea pigs.