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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

May 4, 2001

**MEMORANDUM**

Subject: Acute Toxicity Review
Name of Product: Triticonazole Technical Fungicide
EPA File Symbol: 432-REER
DP Barcode: D272229
Case No: 064944
PC Code: 125620

From: Sidney Jackson, Acting Team Leader
Technical Review Branch
Registration Division (7505C)

To: Summer Gardner, PM Team 21
Fungicide Branch
Registration Division (7505C)

**REGISTRANT:** Rhone-Poulenc Ag Company
2 T. W. Alexander Dr.
Research Triangle Park, NC 27709

**ACTION REQUESTED:** Technical Review Branch(TRB) was asked to review eight acute toxicity studies on a pending pesticide registration, Triticonazole Technical Fungicide, EPA File Symbol 432-REER.

**BACKGROUND**: Rhone-Poulenc AG Company submitted eight acute toxicity studies to support registration of this new active ingredient. The studies were assigned MRID Numbers 448020-28 through -35.

The acute toxicity studies were conducted by the following Laboratories:

1). Life Science Research Ltd.,
2). Springborn Laboratories,
3). Stillmeadow, Inc.,
4). Rhone-Poulenc Agrochimie, and
5). Pharmaco-LSR Ltd.

**CONCLUSIONS AND RECOMMENDATIONS**: TRB has reviewed the eight studies and found them acceptable, with the exception of the two dermal sensitization studies. TRB is unable to accept reported negative findings in these two dermal sensitization studies, mainly, because required positive control studies were not reported.

Registrant must submit an acceptable dermal sensitization study.

The acute toxicity profile for Triticonazole Technical Fungicide, EPA File Symbol 432-REER is as follows:

| | | | |
|---|---|---|---|
| acute oral toxicity | III | Acceptable | MRID 448020-28 |
| acute oral toxicity | III | Acceptable | MRID 448020-29 |
| acute dermal toxicity | III | Acceptable | MRID 450899-30 |
| acute inhalation toxicity | IV | Acceptable | MRID 450899-31 |
| primary eye irritation | IV | Acceptable | MRID 450899-32 |
| primary skin irritation | IV | Acceptable | MRID 450899-33 |
| dermal sensitization | -- | Unacceptable | MRID 450899-34 |
| dermal sensitization | -- | Unacceptable | MRID 450899-35 |

**LABELING**: Based on the toxicity profile above, the following are the precautionary and first aid statements for Triticonazole Technical Fungicide, EPA File Symbol 432-REER, as obtained from the Label Review System.

ID #: 000432-01221 Triticonazole Technical Fungicide

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed or absorbed through skin. Avoid contact with eyes, skin or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF ON SKIN OR CLOTHING: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

The following statement should appear within a USER SAFETY RECOMMENDATIONS box:

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

## DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Cummins, H. A. (1990) RPA 400727; Acute Oral Toxicity in the Rat. Life Science Research Limited, Eye, Suffolk IP23 7PX, England. Laboratory Report Number 90/RHA336/0449. July 20, 1990. MRID 458020-28.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In an acute oral toxicity study, ten young adult rats of the CD strain (remote Sprague-Dawley origin); Weight: Pre-fasted body weight on the day prior to dosing ranged from 103-118 g males; 99-105 g females; Source: Charles River (U.K.) Limited, Margate, Kent, England. Five male and five female rats were given a single oral dose of Triticonazole@92.5% (RPA 400727) at the maximum practicable dosage of 2000 mg/kg. The test substance was administered on day 1 at a volume-dosage of 20 ml/kg in 0.5% w/v methylcellulose in distilled water. Animals were observed for clinical signs of toxicity and mortality for 14 days post dosing.

No mortality occurred. Oral $LD_{50}$ Males and Females = > 2000 mg/kg.

Triticonazole@92.5% is classified as Toxicity Category III based on the $LD_{50}$ value >2000 mg/kg in both sexes of the rat.

Signs of reaction to treatment were confined to decreased motor activity and ataxia in one male and all female animals on day 1. The animals were recovered by day 2 and remained overtly normal throughout the remainder of the observation period. The animals achieved expected body weight gains. Necropsy revealed no significant macroscopic lesion.

This study is classified as "Acceptable (870.1100)" and satisfies the guideline requirement for an acute oral study in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality Statements were provided.

## DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Douds, G. A. (1998) RPA 406203; Acute Oral Toxicity in the Rat. Springborn Laboratories, Inc., Spencerville, Ohio, SLI Study No. 3147.263, December 9, 1998. MRID No.448020-29.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In an acute oral toxicity study, ten young adult Sprague-Dawley rats; Weight: Pre-fasted body weight on the day prior to dosing ranged from 256-273 g males; 220-239 g females; Source: Harlan Sprague Dawley, Inc. Five male and five female rats were given a single oral dose by gavage of Triticonazole@92.5% active ingredient (RPA 406203) at a dosage of 2000 mg/kg. The test substance was administered on day 1 at a volume-dosage of 8 ml/kg from a 25% test article in a corn oil mix. Animals were observed for clinical signs of toxicity and of mortality for 14 days post dosing.

No mortality occurred during the test period. Noted clinical abnormalities observed during testing included decreased defecation, dark material around the facial area and fecal stain.

Body weight gain or maintenance was noted for all animals during the test period. The mean body weight on day 14 for males and females was 303 g and 240 g, respectively.

At necropsy on day 14, four incidences of foci on the lungs of the male rats were observed. However, the toxicological significance of this finding is not clear as untreated animals may show same symptoms.

The acute oral LD50 of Triticonazole@92.5% is estimated to be greater than 2000 mg/kg in the rat, both male and female.

Triticonazole@92.5 is classified as Toxicity Category III based on the acute oral $LD_{50}$ value >2000 mg/kg.

This study is classified as "Acceptable (870.1100)" and satisfies the guideline requirement for an acute oral study in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

**DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200)**

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Johnson, I. R. (1991). RPA400727: Acute Percutaneous Toxicity Study in the Rat. Life Science Research Ltd., Study No. 91/RHA449/0660, September 12, 1991. MRID 448020-30.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In an acute dermal toxicity study, five young adult albino CD strain Sprague-Dawley derived rats/sex; Source: Charles River (U. K.) Limited, Margate, Kent, England, were dermally exposed to a single application of Triticonazole@92.5% active ingredient (RPA400727) at the maximum practicable dosage of 2000 mg/kg (limit test) for 24 hours. The test substance was placed on gauze and moistened with 0.2 ml distilled water before dosing. Animals were observed for clinical signs of toxicity and of mortality in three inspections during the first hour after administration and two further inspections during the remainder of Day 1. From Day 2 through Day 14, the animals were inspected twice daily (morning and afternoon).

Dermal $LD_{50}$ Males = > 2000 mg/kg (observed); Dermal $LD_{50}$ Females = > 2000 mg/kg (observed).

Triticonazole@92.5% is classified as Toxicity Category III based on the observed $LD_{50}$ values in both sexes.

All animals survived. No systemic sign of reaction to treatment was observed. Local signs at site of administration were observed in two female rats. Both animals showed very slight to well-defined erythema and eschar formation between three and ten days after dosing. One of these rats also showed loss of flexibility between three and six days and sloughing between seven and ten days after treatment. The other rat demonstrated slight exfoliation on the sixth and seventh day.

The male rats and the other three female rats showed no local reaction to treatment. All animals gained body weight. Necropsy after Day 15 revealed no significant macroscopic lesions.

This study is classified as "Acceptable (870.1200)" and satisfies the guideline requirements for an acute dermal toxicity study in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (870.1300)

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Bennick, J. E. (1998). Triticonazole; Acute Inhalation Toxicity Study in Rats. Stillmeadow, Inc., Sugar Land, TX. Laboratory Report Number 3925-97, June 8, 1998. MRID No. 448020-31.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In an acute inhalation toxicity study, five young adult albino Sprague-Dawley derived rats/sex (Weight: 301-347 g males; 189-203 g females; Source: Harlan Sprague-Dawley, Inc., Indianapolis, IN) were tested (exposed nose only) for four hours to an aerosol generated from the undiluted test substance (fine powder) at a level of 2.63 mg/L. Observations of mortality and signs of pharmacologic an/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days.

Inhalation $LC_{50}$ for Triticonazole@92.5% > 2.63 mg/L in males and females.

There was no mortality during the study. Clinical signs included activity decrease and piloerection in both sexes. Animals were asymptomatic by Day 3. The inhalation chamber gravimetric mean exposure concentration for Triticonazole@92.5% was calculated at 2.63 mg/L with an average mass median aerodynamic diameter of 2.4 $\mu$m.

Triticonazole@92.5% is classified as Toxicity Category IV based on the observed $LC_{50}$ values in both sexes.

Observations from gross necropsy conducted on each animal at termination of the study revealed no discernible abnormalities; except discolored lungs in one female, not related to test substance administration.

This study is classified as "Acceptable (870.1300)" and satisfies the guideline requirement for an acute inhalation study in the rat.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

## DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400)

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Dange, M. (1997). Triticonazole (RPA400727), Acute Eye Irritation Toxicity Test in the Rabbit. Rhone-Poulenc Agrochimie, Study Number SA96488, January 29,1997. MRID No. 448020-32.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In a primary eye irritation study, six female New-Zealand albino rabbits; Source: Elevage Scientifique des Dombes (E.S.D.), Romans, France, received a single instillation of 100 mg of Triticonazole@92.5% active ingredient product , placed into the left eye conjunctivae sac of each animal. The eyelids were gently held together for approximately one second before releasing. The right eye remained untreated and served as a control. Animals were checked for moribundity and mortality twice daily throughout the study, and examined at least once daily for clinical signs. All animals were observed for ocular irritation at 1, 24, 48 and 72 hours post-instillation.

Triticonazole@92.5% is classified as Toxicity Category IV based on the resolution of ocular irritation by 24 hours.

There was no mortalities during the course of the study. There were no clinical signs or behavioral abnormalities.

Triticonazole@92.5% induced a transient redness to the conjunctivae at one hour after instillation in all animals which disappeared after 24 hours. No corneal, conjunctival or iridial lesions were observed. The test material produced an acute ocular irritation index (AOI) of 2.7, and a mean ocular irritation index (MOI) of 0 after 48 hours resulting in a classification of non-irritant to the rabbit eye according to the Kay and Calandra classification system. Triticonazole@92.5% did not produce positive criteria in any rabbit tested.

This study is classified as "Acceptable (870.2400)" and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

**DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500)**

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Johnson, I. R. (1991). RPA400727: Acute Dermal Irritation/Corrosion Test in the Rabbit. Life Science Research Ltd., Eye, Suffolk IP23 7PX, England. Study Number 91/RHA453/0762, October 15, 1991. MRID No. 448020-33.

**SPONSOR:** Rhone Poulenc Ag Company, 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In a primary dermal irritation study, three young adult New Zealand White strain albino rabbits; (Source: Ranch Rabbits, Crawley Down, Sussex, England) were dermally exposed to Triticonazole@92.5% active ingredient product (RPA400727) for 4 hours. On the dorsum (clipped free of hair) of each test animal between the limb girdles, two test sites (6 x 6 cm) were marked and moistened with approximately 0.2 ml of distilled water. A single dose of 0.5 g Triticonazole@92.5% was applied to the right test site with the left test site serving as the control. Assessment of skin irritation responses at the control and treated test sites were made one hour, 24, 48 and 72 hours after treatment.

Triticonazole@92.5% is classified as Toxicity Category IV based on the absence of dermal irritation symptoms over the 72 hour test period.

No dermal response was observed at the test site of any animal at any time during the 72 hours observation period.

This study is classified as Acceptable (870.2500) and satisfies the guideline requirement for an primary dermal irritation study in the rabbit.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.



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## DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Johnson, I. R. (1993) RPA400727; Delayed Contact Hypersensitivity Study in Guinea Pigs. Pharmaco-LSR Ltd., Eye Suffolk IP23 7PX, England, Study No. 93/RHA500/0071, February 9, 1993. MRID No. 448020-34.

**SPONSOR:** Rhone Poulenc Ag Co., 2 T. W. Alexander Drive, Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** Delayed contact hypersensitivity was assessed using 30 young adult male and female Dunkin Hartley albino guinea pigs (Source: Harlan Olac Limited, Bicester, Oxfordshire, England) by the Magnusson-Kligman Maximization Test. Ten males and ten females received intradermal injections of each of the following three treatments: Freunds Complete Adjuvant; 5% w/v Triticonazole@92.5% active ingredient product (RPA400727) in propylene glycol; and 5% w/v Triticonazole@92.5% in the adjuvant on Day 1. Seven days later the same area of skin was treated by topical application of 50% w/v Triticonazole@92.5% in propylene glycol and the test site was covered by an occlusive dressing for 48 hours. The same induction procedures were carried out on a concurrent control group of ten male and ten female animals, except the test material was replaced by vehicle (propylene glycol) in all doses.

On Day 22, all animals were challenged by occluded application of propylene glycol to the left flank and 50% w/v Triticonazole@92.5% in propylene glycol and 10% w/v Triticonazole in propylene glycol to two sites on the fright flank. The occlusive dressings were removed on the following day and the test sites were scored approximately 24 and 48 hours later.

Repeated administrations of Triticonazole@92.5% did not cause delayed contact hypersensitivity in guinea-pigs. A non-sensitizer classification is proposed for Triticonazole@92.5% based on the results of this study.

Intradermal injection of 5% w/v Triticonazole@92.5% in propylene glycol or the adjuvant caused slight or moderate erythema, pallor and discoloration. Topical application of 50% w/vTriticonazole@92.5% in propylene glycol caused barely perceptible or slight erythema and exfoliation in most animals.

No significant response was observed to challenge with 10% w/v Triticonazole@92 5% in propylene glycol.

A significant response (slight erythema) was observed in three control and no test animals following challenge with 50% w/v Triticonazole@92.5% in propylene glycol. The laboratory considered that the reaction with the control animal was incidental.

This study is classified as unacceptable and does not satisfy the guideline requirements for a dermal sensitization study in the guinea pig for the following reasons:

1. A positive control test must submitted. A positive control test must be conducted within a six month time-period surrounding the main study and conducted in the same manner as the main study. The positive control study must demonstrate sensitization. A successful study demonstrates the lab's ability to properly conduct a sensitization study.

2. Reported test results are suspect because of what appears to be positive responses in the naive control animals. Registrant must submit a valid dermal sensitization study.



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**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

**DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)**

**Product Manager:** 21 **Reviewer:** Sidney Jackson

**CITATION:** Rees, P. B. (1992) RPA400727; Delayed Contact Hypersensitivity Study in Guinea Pigs. Life Science Research Ltd., Study # 92/RHA472/0388, May 29, 1992. MRID No. 448020-35.

**SPONSOR:** Rhone Poulenc Ag Co., 2 T. W. Alexander Dr., Research Triangle Park, NC 27709

**EXECUTIVE SUMMARY:** In a dermal sensitization study on RPA400727 was conducted on ten male and ten female young adult Dunkin Hartley albino guinea pigs (Source: Olac Limited, Bicester, Oxfordshire, England) using a modified version of the method devised by Buehler (1965). Test animals were subjected to six-hour occluded topical application (to shaven left flanks) of 50% w/v Triticonazole@92.5% (RPA4000727) in propylene glycol on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 of the test period. The same induction procedures were carried out on a contemporaneous control group of five male and five female guinea-pigs, except that the test material was replaced by propylene glycol (vehicle) in all doses.

On Day 29, all test and control animals were challenged by six-hour occluded topical applications of 50% and 10% w/v RPA400727 in propylene glycol and propylene glycol alone to their shaven right flanks. Dermal responses to the challenge procedure were assessed approximately 24 and 48 hours after application of the occlusive dressings.

No significant dermal response (faint erythema or a more marked reaction) was observed in test or control animals following challenge with 50% or 10% w/v Triticonazone@92.5% in propylene glycol or propylene glycol alone.

Applications of 50% v/v Triticonazole@92.5%inpropylene glycol caused very faint erythema on one occasion during the first week of inductions and at the majority of application sites during the second and third weeks. Repeated occluded dermal applications of Triticonazole@92.5% did not cause delayed contact hypersensitivity in guinea-pigs. No reaction was observed among the control animals.

An acceptable dermal sensitization study must be submitted. TRB finds the proposed "non-sensitizer" classification of Triticonazole@92.5% based on above test results unacceptable. Study results do not satisfy the guideline requirements for a dermal sensitization study in the guinea pig for the following reasons:

1. Test results from 50% w/v Triticonazole@92.5%in propylene glycol showed signs of erythema at the majority of application sites during second and third weeks are suspect positive indications of dermal sensitization. Recommend using 20% or 30% w/v test material with Buehler Method.

2. A positive control test must submitted. A positive control test must be conducted within a six month time-period surrounding the main study and conducted in the same manner as the main study. The positive control study must demonstrate sensitization. A successful study demonstrates the laboratory's ability to properly conduct a sensitization study.

**COMPLIANCE:** Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

**ACUTE TOX ONE-LINERS**

1. **DP BARCODE:** D272229 **2. PC CODE:** 125620
3. **CURRENT DATE:** April 20, 2001
4. **TEST MATERIAL(s):** Triticonazole (purity 92.5%), RPA400727 and RPA406203

| Study/Species/Lab<br><br>Study # /Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Acute oral toxicity/rat<br>Life Science Research Ltd.<br>90RHA336/0449, 07-20-90 | 44802028 | $LD_{50}$ = >2000 mg/kg (males)<br>= >2000 mg/kg (females) | III | A |
| Acute oral toxicity/rat<br>Springborn Laboratories, Inc.<br>3147.263/12-09-98 | 44802029 | $LD_{50}$ = >2000 mg/kg (males)<br>=>2000 mg/kg (females) | III | A |
| Acute dermal toxicity/rat<br>Life Science Research Ltd.<br>91/RHA449/0660, 09-12-91 | 44802030 | $LD_{50}$ > 2000 mg/kg (males and females) | IV | A |
| Acute inhalation toxicity/rat<br>Stillmeadow, Inc.<br>Study No. 3925-97/06-08-98 | 44802031 | $LC_{50}$ > 2.63 mg/L (males and females) | IV | A |
| Primary eye irritation/rabbit<br>Rhone-Poulenc Agrochime<br>SA96488/01-29-97 | 44802032 | Conjunctivitis in 6/6 eyes at one hour after instillation. All irritation resolved by 24 hours. | IV | A |
| Primary dermal irritation/rabbit<br>Life Science Research<br>91/RHA453/0762, 10-05-99 | 44802033 | No irritation at 72 hours | IV | A |
| Dermal sensitizaton/guinea pig<br>Pharmaco-LSR<br>93/RHA500/0071, 02-09-93 | 44802034 | Test results are suspect, possible sensitizer | -- | U |
| Dermal sensitization/guinea pig<br>Life Science Research Ltd.<br>92/RHA472/0288, 05-29-92 | 44802035 | Test results are suspect, possible sensitizer | -- | U |

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**



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