DATA EVALUATION REPORT (11-15-00)

TRITICONAZOLE

STUDY TYPE: REPEATED DOSE DERMAL – RAT [OPPTS 870. 3200 (82-2)]
MRID 44933601

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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Task Order No. 00-17K

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Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 3 Week Repeated Dose Screening Dermal – Rat [OPPTS 870.3200 (§82-2)]

DP BARCODE: D261924
P.C.CODE.: 125620

SUBMISSION CODE: S568827
TOX. CHEM. NO: none

TEST MATERIAL (PURITY): Triticonazole (97.2%)

SYNONYM: (1RS)-E-2-(4-chlorobenzylidene)-5,5-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentan-1-ol

CITATION: Weiler, M. S. (1997) 3-Week Dermal Toxicity Study with Triticonazole in Rats. Corning Hazleton, Inc., 3301 Kinsman Boulevard, Madison, Wisconsin 53704. Laboratory Project ID CHW 6224-229, July 14, 1997. MRID 44933601. Unpublished.

SPONSOR: Rhone-Poulenc Ag Company, Research Triangle Park, North Carolina

EXECUTIVE SUMMARY: In a 3-week repeated dose dermal toxicity study (MRID 44933601), groups of 5 male and 5 female Crl:CD(SD)BR VAF/Plus rats were treated with Triticonazole (97.2%, Lot No. 9550347) moistened with water. Animals were treated by dermal occlusion for 6-7 hours/day for 23 days at doses of 0, 100, 300, or 1000 mg/kg/day.

There were no treatment-related deaths or signs of systemic toxicity and no treatment-related effects on body weight, hematology, clinical chemistry, or organ weight. No treatment-related dermal irritation was observed, and no treatment-related histopathological effects were noted.

The dermal and systemic NOAELs are the limit dose of 1000 mg/kg/day. Dermal and systemic LOAELs were not identified.

This study is classified as **Acceptable/Guideline** and does satisfy the guideline requirements for a repeated-dose dermal screening study [OPPTS 870.3200 (§82-2)] in rats.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

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MATERIALS AND METHODS

A. MATERIALS

1. Test material: Triticonazole (97.2%)

Synonym: (1RS)-E-2-(4-chlorobenzylidene)-5,5-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol
Description: white powder
Lot/Batch #: 9550347
Purity/Stability: 97.2%/ "on file with Sponsor"
Structure: not provided

2. Vehicle and/or positive control

Vehicle: water pruified by reverse osmosis
Positive control: none

3. Test animals

Species: rat
Strain: Crl:CD(SD)BR VAF/Plus
Age and weight at study initiation: males: approx. 6 weeks, 198-225 g; females: approx. 6 weeks, 142-173 g
Source: Charles River Laboratories, Portage, MI
Housing: 1/cage in stainless steel, screen-bottom cages
Diet: Certified Rodent Diet #5002, PMI Feeds, Inc., *ad libitum*, except during fasting periods
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 19-25°C
Humidity: 50%±20%
Air changes: not stated
Photoperiod: 12 hour light/12 hour dark cycle
Acclimation period: 16 days (animals were acclimated to collars 6 hours/day for the last 3 days of the acclimation period)

B. STUDY DESIGN

1. In life dates

Start: October 30, 1996 End: November 22, 1996

2. Animal assignment

Rats were randomly distributed within the experimental groups (Table 1) using a computer-generated randomization based on body weight.

Table 1. Experimental design

Group	Dose Level (mg/kg/day)	No. of Animals	
		Male	Female
Control	0	5	5
Low-dose	100	5	5
Mid-dose	300	5	5
High-dose	1000	5	5

Data taken from MRID 44933601, pp. 14.

3. Dose selection rationale

"Signs of toxicity were expected at the high-dose level. The low-dose level was anticipated to be a no-effect level. The intermediate dose level was selected as an additional dose for the purpose of evaluating any potential toxicologic effects."

4. Test substance preparation and analysis

The test substance was applied in its neat form moistened with water (approximately 2µL water/mg test material). Applied doses were determined weekly and were based on the most recent individual animal body weight.

Results –
Homogeneity analysis – Homogeneity analysis was not required since triticonazole was applied in its neat form.

Stability analysis – The report states that a sample of triticonazole was tested after the in life phase of the study. Results from this analysis were not provided.

Concentration analysis – Concentration analysis was not required since triticonazole was applied in its neat form.

Homogeneity and concentration analyses were not required. Stability is considered acceptable for the purposes of this study.

5. Dose application

Rats were acclimated to flexible plastic collars 3 days prior to the first dose application. An area of approximately 10% of the total body surface area (25 cm^2) on the

back of each rat was clipped free of hair prior to study initiation and as necessary thereafter. The test material was applied neat to a gauze patch and was moistened with 2μL/mg water. The gauze patch was placed on each animal, secured with nonirritating tape, covered with a latex dental dam, overwrapped with an elastic bandage, and secured with nonirritating tape. The animals were fitted with flexible plastic collars during the exposure period. After 6-7 hours, the collars and dressings were removed and the treated sites wiped with a water-dampened disposable towel to remove residual test material. Animals were treated daily for 23 days. Control animals were treated the same way, except only water was applied to the gauze patch.

6. Statistics

"One-way ANOVA was used to analyze body weights, body weight gain, food consumption, clinical chemistry, hematology, organ weight, organ to body weight ratios, and organ to brain weight ratios. Levene's test was done to test for variance homogeneity." In cases of heterogeneity of variance at $p \leq 0.05$, transformations were used to stabilize the variance. ANOVA was done on homogeneous transformed data. "If the ANOVA was significant, Dunnett's multiple comparison t-test was used for pairwise comparisons between treated and control groups."

C. METHODS

1. Observations

Animals were examined for mortality and signs of toxicity twice daily. Comprehensive clinical examinations were performed weekly during the treatment period.

2. Body weight

Animals were weighed on the day of initial dosing and weekly thereafter.

3. Food consumption

Individual food consumption was recorded weekly.

4. Food efficiency

Food efficiency was not calculated by the study authors.

5. Ophthalmoscopic examination

Ophthalmoscopic examination was not required and was not performed.

6. Blood samples were obtained from the jugular vein of all surviving (fasted) animals on day 24. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		
	(Kaolin-cephalin time)		
x	Erythrocyte morphology		

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium	x	Albumin
x	Chloride	x	Blood creatinine
	Magnesium	x	Blood urea nitrogen
x	Phosphorus	x	Total Cholesterol
x	Potassium	x	Globulins
x	Sodium	x	Glucose
		x	Total bilirubin
	ENZYMES	x	Total serum protein
	Alkaline phosphatase(ALK)		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		
x	Serum alanine amino-transferase (also SGPT)		
x	Serum aspartate amino-transferase(also SGOT)		
x	Gamma glutamyl transferase(GGT)		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase		

7. Urinalysis

Urinalysis was not required and was not performed.

8. Sacrifice and pathology

On day 24, rats that had been fasted overnight were sacrificed with sodium pentobarbital. The CHECKED (X) tissues were preserved in formalin but not processed further. The (XX) organs were embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined. The (*) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	x	Aorta	xx*	Brain
x	Salivary glands	xx	Heart	x	Periph. nerve
x	Esophagus	x	Bone marrow	x	Spinal cord
x	Stomach	x	Lymph nodes	x	Pituitary
x	Duodenum	xx	Spleen	x	Eyes (optic n.)
x	Jejunum	x	Thymus		
x	Ileum				GLANDULAR
x	Cecum		UROGENITAL	xx	Adrenal gland
x	Colon	xx*	Kidneys[a]		Lacrimal gland
x	Rectum	x	Urinary bladder	x	Mammary gland
xx*	Liver[a]	xx*	Testes[a]	x	Parathyroids
	Gall bladder	x	Epididymides	x	Thyroids
x	Pancreas	x	Prostate		
		x	Seminal vesicle		OTHER
	RESPIRATORY	xx*	Ovaries	x	Bone
x	Trachea	x	Uterus	x	Skeletal muscle
x	Lung[a]		Vagina	xx	Skin (treated and untreated)[a]
	Nose				
	Pharynx			xx	All gross lesions and masses[a]
	Larynx				

*Required for subchronic studies based on Subdivision F Guidelines

II. RESULTS

A. OBSERVATIONS

No treatment-related clinical signs were observed. One high-dose female was found dead on day 17; however, the death was not considered treatment-related since no clinical signs were noted and no treatment-related lesions were observed at necropsy. No dermal effects were observed in any rat at any time during the study.

B. BODY WEIGHT

No treatment-related body weight effects were observed.

C. FOOD CONSUMPTION AND EFFICIENCY

1. Food consumption

Food consumption was 14% ($p<0.05$) higher than controls in males in the 100 and 300 mg/kg/day groups at week 1. These increases are not considered treatment-related or toxicologically significant in light of their transitory nature and lack of a dose-response. No other effects were noted.

2. Food efficiency

Food efficiency was not calculated.

D. OPHTHALMOSCOPIC EXAMINATION

Ophthalmoscopic examination was not required and was not performed.

E. BLOODWORK

No treatment-related hematology or clinical chemistry effects were noted.

F. URINALYSIS

Urinalysis was not required and was not performed.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

No treatment-related organ weight effects were noted.

2. Gross pathology

No treatment-related gross lesions were observed.

3. Microscopic pathology

No treatment-related histopathology was observed.

III. DISCUSSION

A. There was no test substance-related mortality during the study. There were no treatment-related signs of systemic toxicity or effects on body weight, hematology, clinical chemistry, or organ weight. No treatment-related dermal irritation was observed, and no treatment-related histopathological effects were noted.

The dermal and systemic NOAELs are the limit dose of 1000 mg/kg/day. Dermal and systemic LOAELs were not identified.

B. STUDY DEFICIENCIES

None identified

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