(11-15-00)

DATA EVALUATION REPORT

TRITICONAZOLE

STUDY TYPE: DERMAL ABSORPTION – RAT (§85-2)
MRID 44802115

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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DATA EVALUATION RECORD

STUDY TYPE: Dermal absorption - Rat [Special Study §85-2)]

DP BARCODE: D261924
P.C. CODE: 125620

SUBMISSION CODE: S568827
TOX. CHEM. NO.:

TEST MATERIAL (PURITY): [^{14}C]-Triticonazole (radiochemical purity>99%)

SYNONYMS: RPA-400727 (phenyl ^{14}C-U)

CITATION: Auger, M. (1996) Triticonazole Formulation: Absorption Study in the Male Rat after Topical Application. Report 96/RHA557/0804. Huntington Life Sciences Ltd., Eye, Suffolk IP23 7PX, England. MRID 44802115. Unpublished.

SPONSOR: Rhône Poulenc Agrochimie, Centre de Recherche, 355 rue Dostoievski, BP 153, F-06903 Sophia Antipolis Cedex, France.

EXECUTIVE SUMMARY: In a dermal penetration study in rats, 120 μL of 15 g/L or 300 g/L solutions of [^{14}C]-Triticonazole (code CMM 2061, lot no. 1191; >99% radiochemical purity) were administered at doses of 0.15 mg/cm^2 (low dose) or 3 mg/cm^2 (high dose) to 12 cm^2 patches of skin (clipped of hair) between the shoulders of male Sprague-Dawley rats. Individual rats were exposed for 8 hours and then the application site was washed. Excreta, blood, skin (treated and untreated), carcass, skin washes, cage wash and apparatus washes were collected at 8, 24, 48, and 72 hours after the 8-hour treatment and were analyzed for radioactivity.

There were no treatment-related deaths or overt signs of toxicity reported. Radioactivity inventory for the preliminary and main study was 98.4 -102% and 99.7 - 100%, respectively. Recovery of radioactivity from individual animals exhibited up to 4-fold differences but such variability can be attributed to the very low quantities absorbed and excreted.

Absorption of the test material following the 8-hour application was minimal (<2% of the total administered dose) regardless of dose. On a percent of administered dose basis, total absorption (determined by assessment of radioactivity from samples of urine, feces, cage wash, expired air [preliminary study only], untreated skin and carcass) was notably less for the high-dose group than for the low-dose group at all time points. Total amount absorbed was similar for the two dose groups. Similarly, blood concentrations at 8, 24, 48, and 72 hours were minimal for the low-dose group and not detectable for the high-dose group. Because of the minimal absorption,

analysis of tissue burdens and distribution was not feasible and inconsequential. Definitive elimination time-course analysis was not possible due to the minimal absorption. The available data, however, suggested that excretion of the small amounts of test material radioactivity via the feces and urine was occurring up to the 72-hour termination of the experiment. Results of the preliminary experiment revealed that expired air was not a consequential route or elimination

Based on the data presented in the reviewed study dermal absorption of the test material is minimal (<2% of the administered dose) at the low and high dose.

This dermal penetration study is **Acceptable/Guideline** and satisfies the requirements for the special study category of dermal absorption [§85-2(f)(2)]. The primary focus of this study type is to ascertain extent of absorption following dermal application followed by washing of the application site. The test article, at the doses tested, was only minimally absorbed over an 8-hour application period with a very small additional absorption from the washed skin. The radioactivity inventory and analyses supported the conclusions of the study author. The study satisfies the requirements of a special dermal penetration study (§85-3(f)(1), OPPTS §870.7600) designed to determine the fate of test material remaining in the washed skin.

COMPLIANCE: Signed and dated GLP and OECD Principles of Good Laboratory Practice (p. 3), Quality Assurance p.4), and Data Confidentiality (p. 2) statements were provided. A Flagging statement was not included.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound

Radiolabeled: [^{14}C]-Triticonazole
Radiochemical purity: >99%
Specific activity: 32 mCi/mmol (1.18GBq/mmol)
Batch/Lot No.: code CMM 2061, Lot No. 1191
Description: bright orange-red opaque liquid
Non labeled: none specified

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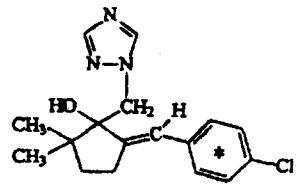
Structure:



* Position of carbon 14 within the ring.

2. Vehicle

The test material was supplied by the sponsor as a suspension in methanol. No reason was supplied forthe use of methanol as a vehicle. The test material is water soluble.

3. Test animals

Species: male CD rat
Strain: Sprague-Dawley
Age and weight at study initiation: age not provided; 180-200 g.
Source: Charles River (UK) Limited, Margate, Kent, England.
Housing: During acclimatization, the rats were housed at a maximum of five/cage in stainless steel type TR18 cages. During the experimental phase, the rats were housed individually in all-glass metabolism cages with metal mesh floors.
Diet: Laboratory Animal Diet No. 1 SQC (Special Diets Services, Witham, Essex, England) was provided *ad libitum.*
Water: tap water (analyzed for chemical contaminants and coliform bacteria) was provided *ad libitum.*
Environmental conditions:
Temperature: 21 °C
Humidity: 55 %
Air changes: 15/hr
Photoperiod: 12 hrs light/12 hrs dark
Acclimation: The rats were acclimatized for at least five days prior to treatment.

4. Preparation of dosing solutions

The Triticonazole-methanol suspensions supplied by sponsor were formulated at 15.0 ± 2.25 g/L and 300 ± 15 g/L. Duplicate samples of the dose formulations were diluted with acetone and analyzed by liquid scintillation counting (LSC). HPLC analysis was also used to confirm purity. Dose formulations were analyzed at pre-study and at dosing.

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Results –

Homogeneity – Data regarding the homogeneity of the dose preparations were not provided.

Stability – Data regarding the stability of the test material as applied to the test species were not provided.

Dose confirmation – The radiochemical purity of the test material at each dose was confirmed by TLC and HPLC and found to be 96.88 - 98.54% (TLC) and 96.76 - 99.41% (HPLC). Achieved doses for each dose regimen were provided and were within 3% of the target dose.

B. STUDY DESIGN AND METHODS

1. Group arrangements

Groups of four rats were assigned to the test groups in Table 1. The rats were observed twice daily. Both a preliminary study (two groups of three rats each) and main (definitive) study (six groups of four rats each) were conducted. Both studies involved an 8-hour application period. In addition to biological samples, components of the application/treatment apparatus (saddle, gauze covers, tape, pipettes, etc.) were retained for analysis.

TABLE 1. Study design for dermal absorption of [^{14}C]-Triticonazole

Experimental Group	Dose mg/cm^2	No./Sex	Comments
Preliminary Group1 Group2	 0.15 3.0	 3 males 3 males	Preliminary assessment of excretory routes. Urine, feces, cage wash, and expired CO_2 and volatile organics collected at 0-24 and 24-48 hrs.
Main low-dose Group3 Group4 Group5	 0.15 0.15 0.15	 4 males 4 males 4 males	Assessment of mass balance. Urine, feces, carcass/skin, and cage wash collected at specific intervals and time points. (See §B.2).
Main high-dose Group 6 Group 7 Group 8	 3.0 3.0 3.0	 4 males 4 males 4 males	Assessment of mass balance. Urine, feces, carcass/skin, and cage wash collected at specific intervals and time points. (See §B.2).

Information taken from pp. 19-20, MRID 44802115.

2. Dosing and sample collection

The test material was applied to a 12 cm^2 area of shaved skin on the dorsal surface of the rat. A silicone rubber saddle attached with cyanoacrylate adhesive was applied prior to the application of the test material. The application pipette was rinsed with acetone and the rinse and pipette retained for assessment of residual radioactivity.

The application site was semi occluded with a stainless steel gauze pad. Nominal doses were 0.15 and 3 mg/cm^2. At the end of the 8-hour application period, the gauze pad was retained and the test application site swabbed with an aqueous solution of 1% Tween 80. For rats providing samples exceeding 8 hours, the removed initial gauze pad was replaced with a clean pad. Blood samples were taken while the rats were under halothane anesthesia. At termination of the experimental period, test animals were killed by an overdose of halothane.

Expired CO_2 - Expired CO_2 was collected in a series of two traps containing 200mL of 2 M sodium hydroxide. The traps were sampled at 0-24 and 24-48 hours and duplicate samples analyzed by LSC. Subsamples of the trap fluids were stored at 4°C.

Volatile organics - Volatile organics were trapped by passing expired air through two traps containing 200 mL of 2-ethoxyethanol. The traps were sampled at 0-24 and 24-48 hours and duplicate samples analyzed by LSC. Subsamples of the trap fluids were stored at 4°C.

Blood - Blood was collected from the retro-orbital sinus of anesthetized rats at the end of the exposure period. The samples were collected into vials containing lithium heparin. The samples were stored at -20°C.

Urine - Urine was collected over 0-24 and 24-48 hours from rats in the preliminary study. For the definitive study, urine samples were collected at 4 and 8 hours for Groups 3 and 6, at 4, 8, 12, and 24 hours for Groups 4 and 7, and at 4, 8, 12, 24, 48, and 72 hours from Groups 5 and 8. The samples were collected over ice and stored at -20°C.

Feces - Feces were collected over 0-24 and 24-48 hours from rats in the preliminary study. For the definitive study, fecal samples were collected 8 hours for Groups 3 and 6, at 8 and 24 hours for Groups 4 and 7, and at 8, 24, 48, and 72 hours for Groups 5 and 8. The samples were collected over ice and washed with distilled water:methanol (1:1, v/v) and stored at -20°C. The washings were also retained for analysis.

Carcass/skin - Following over anesthetization, skin from the treated surface and 1 cm surrounding the treatment area was removed and stored at -20°C prior to analysis. The carcasses were also retained and stored frozen prior to analysis.

Cage wash - Cage wash was retained for analysis.

Unabsorbed dose (non-biological samples) - At termination of the exposure period, the application apparatus (saddle, gauze covers) was removed and retained for analysis of radioactivity. The application site was swabbed with an aqueous solution of 1% Tween 80, the wash collected and the swabs retained for analysis of radioactivity.

4. Sample preparation/analysis

Expired CO_2 - Duplicate weighed samples (~0.25 g) from the CO_2 traps in the preliminary experiment were added to scintillation fluid and counted. Because radioactivity in the CO_2 traps was not above background, CO_2 collection and analysis was not continued in the definitive (main) experiment.

Volatile organics - Duplicate weighed samples (~0.25 g) from the volatile organics traps in the preliminary experiment were added to scintillation fluid and counted. Because radioactivity in the volatile organics traps was not above background, collection and analysis of expiratory products was not continued in the definitive (main) experiment.

Blood - Whole blood samples were thawed to room temperature and duplicate aliquots (~0.1 g) were solubilized prior to LSC analysis.

Urine - Thawed urine samples were weighed and duplicate aliquots (~0.25 g) added to scintillation fluid and analyzed by LSC.

Feces - Feces were thawed, weighed, and homogenized in measured quantities of distilled water. Duplicate weighed aliquots of the homogenate (~0.25 g) were combusted and analyzed by LSC.

Carcass/skin - The treated skin was solubilized and duplicate weighed aliquots (~0.2 g) analyzed by LSC. The residual carcass (minus skin) was thawed, weighed, and homogenized in a measured amount of distilled water. Duplicate aliquots of the homogenate (~0.25 g) were solubilized and analyzed by LSC. The untreated skin was thawed and solubilized. Duplicate samples (~1 g) were analyzed by LSC.

Cage wash - Subsequent to thawing, duplicate aliquots of cage wash samples (~0.25 g) were analyzed by LSC.

Unabsorbed dose (non-biological samples) - The gauze, tape, and other apparatus were washed and sonicated (1 hr) in acetone. The wash was weighed and duplicate aliquots (~0.2 g) were analyzed by LSC. Skin swabs used for cleaning the application site underwent Soxhlet extraction in acetone for 3 hours. The extracts were weighed and duplicate aliquots (~0.2 g) were analyzed by LSC.

5. Analytical techniques

Liquid Scintillation Counting LSC - Either Lumagel, Hionic-Fluor, or Permafluor E^+ scintillation fluids were used. Samples were counted following direct addition to the scintillation fluid or after pretreatment. The samples were solubilized in Soluene-350 followed by decolorization with hydrogen peroxide/propanol, and mixing with Hionic-Fluor and 2 M aqueous sodium hydroxide: methanol (1:1, v/v). Another of the pretreatments was combustion using Combusto-cones and Combusto-pads and

trapping of resultant $^{14}CO_2$ in Carbo-sorb and addition to Permafluor E$^+$ scintillation fluid. An LKB Rackbeta 1219 Spectral scintillation spectrophotometer (Pharmacia/LKB, Milton Keynes, Bucks) with quench correction was used for LSC analysis. Limit of detection was established so that there was a 99% certainty that samples with a mean value greater than the detection limit contained radioactivity of the test material.

Thin Layer Chromatography (TLC) - TLC plates were analyzed using a Raytest RITA linear analyzer (LabLogic Ltd., Sheffield, South Yorks). The TLC stationary phase was silica gel and the mobile phase was heptane:ethyl acetate:methanol (45:45:10, v/v/v).

High Performance Liquid Chromatography (HPLC)- HPLC was performed using an HP 1050 Series system (Hewlett Packard Ltd., Wokingham, Berks) and a RAMONA-LS radiodetectors (LabLogic, Ltd., Sheffield, South Yorks). Two HPLC methods were used. Method 1 (used in the preliminary study) used a Spherisorb silica column (15 cm x 4.6 mm) an isocratic mobile phase of iso-octane:dichloroethane:propan-2-ol:triethylamine (760:200:40:0.5, v/v/v/v) at 1 mL/min and UV detection at 245 nm. Method 2 (used in the main study) utilized a Nucleosil ODS 25 cm x 4.6 mm columns and an isocratic delivered mobile phase of acetonitrile:water (65:35, v/v) at a flow rate of 1 mL/min. Detection was at 230 nm. Both methods used a RAMONA LS radiodetector.

6. Statistics

Some data were presented as means and associated variability. No additional statistical procedures were described.

II. RESULTS

A. PRELIMINARY STUDY

Results of the preliminary study showed acceptable recovery (98.4 -102%) of administered radioactivity over the 48-hour time period (Table 2.). These values represent the mean (± standard deviation) recoveries from three male rats. Recoveries among excretory samples from individual animals exhibited up to 4-fold differences.

B. DEFINITIVE STUDY

1. Radioactivity inventory

Radioactivity inventory is summarized in Table 2. Recovery of administered radioactivity over the 72-hour time period of the main study was 99.7 - 100%. All tabled values for the main study are mean ± standard deviation recoveries from four male rats. Recoveries among excretory samples from individual animals did not

appear to exhibit the level of variability observed for the preliminary study. Recovery from a specific sample did not vary by more than 2-fold among the individual rats.

TABLE 2. Recovery (% of administered dose) of radioactivity from rats following a single dermal application of [^{14}C]-Triticonazole

Sample	Preliminary study (48 hrs)		Main study (72 hrs)	
	low dose	high dose	low dose	high dose
Urine	0.64±0.45	0.07±0.01	0.48±0.10	0.06±0.01
Feces	0.81±0.38	0.10±0.05	1.31±0.45	0.14±0.02
Cage wash	0.07±0.03	0.01±0.01	0.13±0.04	0.05±0.01
CO_2	0.01±0.01	0.02±0.01	-[a]	-[a]
Volatile organics	0.00±0.00	0.01±0.01	-[a]	-[a]
Skin swab/gauze wash	62.7±2.54	96.7±0.39	63.9±4.52	94.1±2.11
Skin				
treated	33.3±1.69	4.93±0.0.67	32.7±4.11	9.46±1.21
untreated	0.07±0.02	0.02±0.02	0.16±0.13	0.01±0.00
carcass	0.81±0.18	0.12±0.04	1.06±0.30	0.08±0.01
Total recovered	98.4±0.49	102±0.29	99.7±2.69	104±1.27

[a] CO_2 and volatile organics not collected in main study.
Data taken from Tables 1, 2, 5, and 8, pp. 31, 32, 35, and 38, MRID 44802115.

2. Absorption

Absorption of dermally applied test material was minimal as implied by the recovery of radioactivity (Table 2) from all potential excretory routes (urine, feces, expired air, cage wash). Based on radioactivity in these samples 48 hours after test article application, absorbed radioactivity represented 1.53 and 0.21% of the administered dose in the low and high-dose groups of the preliminary study. For the main study (which did not evaluate expired CO_2 and volatile organics), these excretory samples represented 1.92 and 0.25% of the administered radioactivity 72 hours after application.

TABLE 3. Fecal and Urinary Excretion (% of administered dose) of radioactivity from rats following a single dermal application of [^{14}C]-Triticonazole				
Sample	Preliminary study (48 hrs)		Main study (72 hrs)	
	low dose	high dose	low dose	high dose
Urine				
0 - 24 hrs	0.45±0.39	0.05±0.01	-	-
24 - 48 hrs	0.19±0.07	0.02±0.00	-	-
Feces				
0 - 24 hrs	0.39±0.17	0.04±0.00	-	-
24 - 48 hrs	0.42±0.22	0.06±0.05	-	-
Urine				
0 - 4 hrs	-	-	0.01±0.01	0.01±0.00
4 - 8 hrs	-	-	0.01±0.01	0.00±0.00
8 - 12 hrs	-	-	0.02±0.00	0.00±0.00
12 - 24 hrs	-	-	0.07±0.01	0.01±0.00
24 - 48 hrs	-	-	0.14±0.03	0.02±0.01
48 - 72 hrs			0.22±0.05	0.02±0.00
Feces				
0 - 8 hrs	-	-	0.00±0.00	0.00±0.00
8 - 24 hrs	-	-	0.16±0.16	0.03±0.01
24 - 48 hrs	-	-	0.74±0.22	0.04±0.02
48 - 72 hrs	-	-	0.41±0.31	0.07±0.02
Total excreted	1.45	0.17	1.79	0.20

Data taken from Tables 1, 2, 5, and 6, pp. 32, 33, 35, and 36, MRID 44802115.

Blood concentrations at 8, 24, 48, and 72 hours are shown in Table 3. Measurement was possible for the low dose group only but the radioactivity detected was only marginally distinguishable from that of background.. The low to nondetect levels in the blood are consistent with the excretion data implying only minimal absorption.

TABLE 4. Concentrations (expressed as ng equivalents/g blood) of [^{14}C]-Triticonazole in blood of rats following a single dermal application		
Time (hrs)	Low dose	High dose
8	3.9±5.1	ND
24	9.0±2.6	ND
48	7.5±13.0	ND
72	27.4±11.4	ND

ND: not detected

Data taken from Tables 9 and 10, pp. 39 and 40, MRID 44802115.

Absorption rate was calculated based upon percent absorption values for urine, feces, cage wash, carcass, untreated skin, the total administered dose, and the time period of

concern (Table 4). For the low-dose group, the absorption rate appeared to be rather constant but slow over the time periods studied. For the high-dose group, initial absorption (over the first 8 hours) was more rapid than that exhibited for subsequent time periods. The 2 to 8-fold increased rate for the high-dose group relative to that of the low-dose group did not correspond to the 20-fold difference in dose level, thereby implying a saturation of absorption at the high dose.

TABLE 5. Absorption of [^{14}C]-Triticonazole in rats following a single dermal application

Time (hrs)	low dose		high dose	
	ug	ug/hr	ug	ug/hr
0 - 8	10.0	1.25	70.0	8.75
0 - 2	19.9	0.83	160.0	6.67
0- 48	38.8	0.83	109.9	2.29
0 - 72	59.8	0.83	120.2	1.67

Data taken from Tables 1-8, pp. 31-38 and p. 29, MRID 44802115.

3. Tissue distribution

Tissue distribution was not assessed. Definitive and meaningful assessment of tissue distribution would not have been feasible due to the minimal absorption of the test article.

4. Excretion

Based upon recovery of radioactivity, the small amounts of absorbed test material were excreted via the feces and urine. Results of the preliminary study indicated that expired air was not a significant route of elimination. Total excretion via the feces and urine (and including cage wash) represented 0.18 - 1.92% of the administered dose (Table 2).

Excretion via the feces accounted for somewhat greater amounts of radioactivity than did elimination via the urine (Table 2). Even fecal excretion, however, was minimal (representing no more than 1.31% of the administered dose at 72 hours post-application) due to the limited absorption of the test material. Analysis of 72-hour time-course data (Table 2) indicated that most fecal excretion occurred at 24-72 hours after administration. Variability in excreted radioactivity was observed among individual rats but did not appear to be inconsistent with normal variability in excretory function. Rats in the high-dose groups excreted a lesser percentage of the administered dose than did rats in the low-dose groups. However, considering a 20-fold difference in dose, there was only a 2 to3-fold difference in the overall amount of test article radioactivity that was excreted. This is expected as absorption is a

saturatable process with the qwuantity absorbed increasing to a lessor extent with the increase of dose. This relationship was unaffected over the time periods of the preliminary (48 hours) and main studies (72 hours).

Urinary elimination accounted for only 0.06 - 0.64% (0.11 - 0.71% including cage wash) of the administered dose (Table 2). Time-course analysis of urinary excretion did not reveal any specific temporal pattern in the preliminary study. For the main study, a greater amount of urinary excretion of radioactivity appeared to occur at 24-72 hours.

III. DISCUSSION

A. DISCUSSION

In a dermal penetration study in rats, 120 μL of 15 g/L or 300 g/L solutions of [^{14}C]-Triticonazole (code CMM 2061, lot no. 1191; >99% radiochemical purity) were administered at doses of 0.15 mg/cm^2 (low dose) or 3 mg/cm^2 (high dose) to 12 cm^2 patches of skin (clipped of hair) between the shoulders of male Sprague-Dawley rats. Individual rats were exposed for 8 hours and then the application site was washed. Excreta, blood, skin (treated and untreated), carcass, skin washes, cage wash and apparatus washes were collected at 8, 24, 48, and 72 hours after the 8-hour treatment and were analyzed for radioactivity.

There were no treatment-related deaths or overt signs of toxicity reported. Results of both the preliminary and main study showed acceptable recovery of 98.4 -102% and 99.7 - 100%, respectively, of the administered doses. Recoveries among excretory samples from individual animals exhibited up to 4-fold differences but such variability can be attributed to the very low quantities absorbed and excreted.

Absorption of the test material following the 8-hour application was minimal (<2% of the total administered dose). On a percent of administered dose basis, total absorption (determined by assessment of radioactivity from samples of urine, feces, cage wash, expired air [preliminary study only], untreated skin and carcass) was notably less for the high-dose group than for the low-dose group for all time points. Similarly, blood concentrations at 8, 24, 48, and 72 hours were minimal for the low-dose group and not detectable for the high-dose group. The calculated absorption rates indicated that considerably less than 0.1% of the dose was absorbed per hour. Because of the minimal absorption, analysis of tissue burdens and distribution was not feasible. Elimination time-course analysis was also difficult due to the minimal absorption. The available data, however, suggested that excretion of administered radioactivity via the feces and urine was occurring up to the 72-hour termination of the experiment.

Based on the data presented in the reviewed study, it appears that the dermal absorption of the test material is minimal at both the low dose and high dose. On a percent of administered dose basis, greater absorption and excretion was observed for the low-dose group. However, on the basis of total amount absorbed and excreted (product of percent

recovered and total administered), there was not a notable difference. The data suggest saturation of absorption at the high dose.

This dermal penetration study is **Acceptable/Guideline** and satisfies the requirements for the special study category of dermal absorption [§85-2(f)(2)]. The primary focus of this study type is to ascertain extent of absorption following washing of the site of dermal application. The results of the reviewed study clearly indicated that the test article, at the doses tested, was only minimally absorbed over the application period. The radioactivity inventory and analyses supported the conclusions of the study author. The study satisfies the requirements of a dermal penetration study (§85-3(f)(1), OPPTS §870.7600).

B. STUDY DEFICIENCIES

Data regarding the stability of the dosing preparations were not provided. It is assumed that the test material preparations were properly stored and that no significant degradation was occurring during the test period. However, it is suggested that the registrant submit a statement regarding stability of the test article preparation as applied to the test animals.

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