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

OFFICE OF PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

TXR: 0053809

DATE: May 30, 2006

SUBJECT: ***Propiconazole***- Review of dermal Absorption Studies
PC Code: 122101 Reregistration Case #: 3125

FROM: Abdallah Khasawinah, Ph.D.
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Susan Hummel
Reregistration Branch 4
Health Effects Division (7509C)

TO: Christina Scheltema
Chemical Review Manager
Reregistration Branch 3,
Special Review and Reregistration Division (7508W)

TASK ID: DP Code D 322588

Action Requested: Review *in vivo* and *in vitro* penetration studies submitted by the registrant Syngenta Crop Protection – MRID 46250701 and 46250702

Agency's Action:

MRID 46250702 is an *in vivo* dermal absorption study in male rats administered [phenyl-U-^{14}C] CGA 64250 (formulated as TILT$^{®}$250 EC) at three doses to approximately 10 cm^2 of body surface for 6 hour exposure and monitored up to 48 hr post-dosing. Absorbed radioactivity ranged from 7-17% of the administered dose after 6 hours of dermal exposure. However, this exposure period does not meet the EPA guidelines for deriving an absorption factor. Therefore this study is considered **Acceptable/Non-Guideline** and is supplementary to an **Acceptable/Guideline** Study (MRID 00164469).

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MRID 46250701 is an *in vitro* dermal absorption study in epidermal membranes prepared from rat and human (cadaver) abdominal skin to which was applied [phenyl-U-^{14}C] CGA 64250 (formulated as TILT®250 EC). Percutaneous absorption was assessed over 48 hours. The transfer of test article across the epidermal membranes was greater for the rat epidermal preparation than for the human epidermal preparation. This *in vitro* percutaneous absorption study is a specialty study not designed to satisfy OPPTS 870.7600:(§85-3) guidelines and is classified as **Acceptable/Non-Guideline**.

The DER of these studies is attached to this memo.

EPA Reviewer: Abdallah Khasawinah, Ph.D.
Reregistration Branch 4, Health Effects Division (7509C)
EPA Secondary Reviewer: Rebecca Daiss
Reregistration Branch 4, Health Effects Division (7509C)

Signature: A. Khasawinah
Date 5-30-2006
Signature: Becky Daiss
Date 5/30/06

TXR#: 0053809

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Rodent *In Vivo* Dermal Penetration Study - *Rat,* OPPTS 870.7600 [§85-2]; OECD none. *In Vitro* Percutaneous Absorption through Rat and Human Epidermis.

PC CODE: 122101 **DP BARCODE:** DP322588

TEST MATERIAL (PURITY): Phenyl-U-^{14}C CGA 64250 (98.9% a.i.)

SYNONYMS: Propiconazole; TILT® 250 EC (A-6097 K), Banner®, 1-[[2-(2',4'-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]-methyl]-IH-1,2,4-triazole

CITATION: Hassler, S. (2000) Dermal Absorption of (Phenyl-U-(Carbon 14)) CGA 64250 Formulated as Tilt 250 EC (A-6097 K) in the Rat. Novartis Crop Protection, AG. CH-4002 Basel, Switzerland. Project Number: 044AM01. MRID: 46250702 Unpublished 60 p.

Hassler, S. (2000) The *in vitro* Percutaneous Absorption of (Phenyl-U-(Carbon 14)) CGA 64250 Formulated as Tilt 250 EC (A-6097 K) through Rat and Human Epidermis. Novartis Crop Protection, AG. CH-4002 Basel, Switzerland. Project Number: 044AM02. MRID: 46250701 Unpublished 59 p.

SPONSOR: Syngenta Crop Protection, Inc.410 Wing Road, Greensboro, NC 27419

EXECUTIVE SUMMARY: *In vivo* and *in vitro* studies were conducted to examine the dermal absorption of CGA 64250 (propiconazole).

In an *in vivo* dermal absorption study (MRID No. 46250702), male Tif: RAI f (SPF) rats were administered nominal doses of 0.6, 6.0 or 2300 µg/cm^2 of [phenyl-U-^{14}C] CGA 64250 (formulated as TILT®250 EC) to approximately 10 cm^2 of body surface for 6 hour exposure and monitored up to 48 hr post-dosing. Mean dermal absorption values after 6 hours of exposure were 12, 17 and 7% of the applied dose at the low-, mid- and high dose, respectively. Mean radioactivity (percent of the applied dose) remaining at the skin site at 48 hour sacrifice was 7.66%, 5.63% and 1.81%, respectively at the three dose levels. The low absorption rate at the high dose demonstrates saturated absorption. The dislodged residues removed by washing the

treated site after 6 hours was highest at the high dose (~73%, 70%, 91% at the low-, mid- and-high dose, respectively). The absorbed radioactivity was excreted nearly equally in the urine and feces. Insignificant amounts of radioactivity were detected in the carcass after 48 hours of exposure in all of the doses, suggesting complete excretion. The absorbed amounts of radioactivity per cm^2 were 0.074, 0.083 and 0.100 ug/cm^2 for the low dose; 1.01, 1.36, and 1.26 ug/cm^2 for the mid dose and 159, 111, and 130 ug/cm^2 for the high dose at 6, 24, and 48 hour intervals, respectively. The penetration rate for the exposure period of 6 hours was calculated to be 0.012, 1.69, 26.5 ug/cm^2 /hr at the low, mid and high doses, respectively. The nearly 4000 fold higher concentration at the high dose level led only to 2000 fold higher penetration rate as compared to the low dose level. Time-course data for blood samples from rats in mid- and high-dose 48 hour subgroups revealed that radioactivity in the blood increased rapidly with a T_{max} of 2 to 6 hours. In the low dose groups blood residues were non-detectable.

This study was conducted at test concentrations (low and mid dose) to reflect typical concentrations recommended in the field. The exposure time of 6 hours was chosen to reflect the OECD guidelines based on anticipated exposure period of a plant and field worker. However, this exposure period does not meet the EPA guidelines of using several exposure periods including a 10 hour duration, where such duration is used to derive an absorption rate for a typical work day in the USA. Therefore this study (MRID 46250702) although scientifically acceptable, it does not meet the EPA guideline OPPTS 870.7600 for a dermal penetration study and is considered **Acceptable/Non-Guideline**. However, the findings in this study are consistent with results obtained from an **Acceptable/Guideline** Study (MRID 00164469) where the absorbed dose at 2 and 4 hour exposures was within the range of the absorbed dose after 6 hours exposure in the current study. A longer exposure duration to 10 hours in MRID 00164469 study resulted in higher absorption indicating that in the current study under review if exposure duration was extended to 10 hours, absorbed values would be comparable to the MRID 00164469 study.

The percutaneous absorption study (MRID 46250701) utilized epidermal membranes prepared from rat and human (cadaver) abdominal skin to which was applied 0.56, 5.2 or 2165 $\mu g/cm^2$ [phenyl-U-^{14}C] CGA 64250 (formulated as TILT®250 EC). Percutaneous absorption was assessed over 48 hours. Under the conditions of this study, species variability (rat vs human) in the percutaneous absorption of CGA 64250 is clearly indicated. The transfer of test article across the epidermal membranes was notably greater for the rat epidermal preparation than for the human epidermal preparation; flux values were considerably greater (95-fold for the low dose, 17-fold for the mid dose and 11-fold for the high dose) for the rat epidermal preparation compared to human dermal preparation. In comparing the different doses, flux increased proportionally with increased dose for rat and human skin. Flux was 1.81, 1.994, 76.2 $\mu g/cm^2$/hr for the rat, and 0.019, 0.107, 6.988 $\mu g/cm^2$/hr for the human skin at the low-, mid- and high-dose, respectively resulting in greater absolute amounts of test article being transferred across the epidermal membranes at the high dose but resulting in a decrease in percutaneous absorption expressed as per cent of applied dose. It is apparent that percutaneous absorption at the high application level represented saturation. This *in vitro* percutaneous absorption study is a specialty

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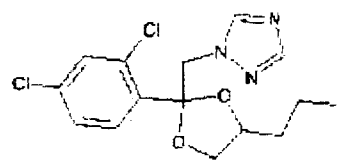
study not designed to satisfy OPPTS 870.7600;(§85-3) guidelines and is classified as **Acceptable/Non-Guideline**. U.S. EPA has insufficient information to show that the existing *in vitro* procedures accurately predict *in vivo* dermal penetration of chemicals. None of the numerous methods used for *in vitro* studies have been validated, i.e., U.S. EPA has a limited data base which indicates that *in vitro* data do not produce quantitative data that accurately match the *in vivo* dermal penetration data (Zendzian and Dellarco, 2003 in "Alternative Toxicological Methods" edited by Salem and Katz, Pages 207-219, CRC Press). Therefore, EPA does not currently use *in vitro* studies in risk assessment.

COMPLIANCE: Signed and dated GLP (in compliance with GLP in Switzerland, Procedures and Principles of 1986 based on OECD Principles of GLP adopted May 1981 by Decision of the OECD Council [C (81) 30 (Final)] concerning Mutual Acceptance of Data in the Assessment of Chemicals), Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	Phenyl-U-^{14}C CGA 64250
Description:	colorless clear viscous liquid
Lot/Batch #:	Radiolabel: ILS-229.1; Non-radiolabel: AMS 181/7
Purity:	Radiolabel: 98.9%; Non-radiolabel: 98.2% a.i.
Compound Stability:	expiration date May 30, 1999 for radiolabeled and Feb. 2005 for the non-radiolabeled.
CAS # for TGAI:	60207-90-1
	
Vehicle/Solvent used:	
Radiolabelling:	Uniformly labeled ^{14}C Phenyl
Specific Activity:	Specific activity 2840 Kbq/mg (76.8 uCi/mg)
Radiochemical Purity:	
Source:	Dr. P.Ackermann, Isotope Laboratory, Novartis Crop Protection AG, CH-4002 Basel, Switzerland
Other comments:	

2. Relevance of Test Material to Proposed Formulation(s):

The test substance was formulated according to protocol A-6097 K.

3. Test animals:		
Species:	1) Rats 2) rat and human abdominal skin	
Strain:	1) Tif: RAI f (SPF) 2) epidermal membrane from Tif: RAI f (SPF) rat;	
Age/weight at study initiation:	1) 8 weeks male rats about 250 g 2) rats: 23 days at time of preparation of epidermal membrane human skin: male and female donors, aged 52 and 76 years, respectively	
Source:	1) Rats: RCC Ltd., Biotechnology & Animal Breeding Division, Fullinsdorf, Switzerland 2) human skin: obtained from cadavers (Caucasian); Institut für Pathologie, Kantonsspital Basel, Basel, Switzerland	
Housing:	Rats housed individually in Plexiglass metabolism cages	
Diet:	Certified standard diet (Nafag No. 8900; NAFAG, Gossau, Switzerland) ad libitum	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20-22 EC
	Humidity:	44-56 %
	Air changes:	Not reported
	Photoperiod:	12 hrs dark/ light
Acclimation period:	At least 5 days including one day in the metabolism cage with shaved dorsal area of 25-35 cm^2	

B. STUDY DESIGN: The experimental designs for MRID 46250702 and 46250701 are summarized in Table 1.

TABLE 1. Study design for dermal penetration of Phenyl-U-^{14}C CGA 64250.

Test Group	No. of rats	Target Dose[b] ($\mu g/cm^2$)	Actual dose ($\mu g/cm^2$)	Comments
In Vivo Male Rat Study MRID 56250702				
Low dose 6 hour exposure	4 4 4	0.6 (16 kBq/animal) 0.6 (16 kBq/animal) 0.6 (16 kBq/animal)	0.58 0.58 0.58	termination at 6 hrs after application termination at 24 hrs after application termination at 48 hrs after application
Mid dose 6 hour exposure	4 4 4	6.0 (171 kBq/animal) 6.0 (171 kBq/animal) 6.0 (171 kBq/animal)	6.02 6.02 6.02	termination at 6 hrs after application termination at 24 hrs after application termination at 48 hrs after application
High dose 6 hour exposure	4 4 4	2300 (921 kBq/animal) 2300 (921 kBq/animal) 2300 (921 kBq/animal)	2327 2327 2327	termination at 6 hrs after application termination at 24 hrs after application termination at 48 hrs after application
In Vitro Dermal Penetration Study MRID 56250701				
Rat epidermis Q1A1 Q1A2 Q1A3		 0.56 5.2 2142	 0.56 5.2 2142	Percutaneous penetration of rat dermal membrane (MRID 46250701); perfusates collected at 0-6, 6-24, and 24-48 hrs
Human epidermis Q2A1 Q1A2 Q1A3		 0.56 5.2 2165	 0.56 5.2 2165	Percutaneous penetration of human dermal membrane (MRID 46250701); perfusates collected at 0-6, 6-24, and 24-48 hrs

Information taken from p. 18 and pp. 35-37of MRID 46250702, and pp. 19- 20, MRID 46250701

1. Dose

Rationale: Dose selection was based on typical concentrations recommended for the use in stone fruits (94 g a.i./1500 L applied to one hectare) for the low and mid dose groups as well as the undiluted formulation (250 a.i./L) for the high dose group. Additional dose information (number of animals, dose duration, skin wash time, termination time, etc.) is summarized in Table 1.

Dose volume: 10 $\mu L/cm^2$ skin

Duration of exposures (time from dose to skin wash): **6 hours**

Termination periods (time from dose to sacrifice): 6, 24 or 48 hours

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At the end of the 6 hour exposure period the test substance remaining on the test site was removed from the skin by washing 5 times with a mild soap solution (Lux shower gel: 40 g/L, pH 5.0) using cotton swabs.

Number of animals/group: 4 rats/time point/dose

2. Animal/Membrane Preparation

In MRID 46250702, one day prior to application of the test material, a dorsal area of 25-35 cm^2 was shaved with an electric clipper taking care not to abrade the skin. Animals with damaged skin were not used. There was no indication in the study report if the shaved area was washed. Prior to dosing, a double Viton rubber 'O'-ring glued on top of each other with an inside area of approximately 10 cm^2 was glued to the shaved skin with cyanoacrylate and a permeable tape included as part of the non-occlusive cover on the application site. To protect the application site, a collar was placed on each animal's neck.

In the *in vitro* study (MRID 46250701), rat and human epidermis were obtained from abdominal skin samples. The rat skin was soaked in aqueous 2M sodium bromide containing 0.01% sodium azide for ~18 hours after which it was blotted dry and the epidermal layers separated. The epidermis was wrapped in aluminum foil and stored at 4°C until used (up to 3 days). Human epidermis was obtained from frozen skin samples allowed to thaw at room temperature. A skin area of ~10 cm^2 was immersed in hot water (60°C) for 1 minute, blotted dry, and the epidermis/dermal layers separated. Circles (1.8 cm diameter) of the epidermal membranes were cut and placed in the diffusion cells between the donor and receptor chambers (14 cells for rat and 7 cells for human), and the cells connected to a peristaltic pump. The membrane/cell apparatus was equilibrated for 0.5 to 1 hour by pumping physiological saline (0.9% NaCl with 0.001 mg/ml tetracycline HCl) at a flow rate of ~3 ml/hr. The integrity of the rat and human epidermis membranes was determined by permeability coefficients (Kp) of tritium water prior to application of the test article. The Kp values for the rat and human epidermal preparations were 1.57-2.08 x 10^{-3} and 1.26-1.56 x 10^{-3} cm/hr. respectively.

3. Dose Preparation, Administration and Quantification:

Preparation: For the *in vitro* and *in vivo* studies, Phenyl-U-^{14}C CGA 64250 and unlabeled CGA 64250 (only high dose group) were mixed with the formulation ingredients (blank formulation). The formulation was prepared separately for all dose levels as shown in Table 2. The stability and homogeneity of the formulated test substance in the application solution was determined by TLC at the time of application. The test substance in the application solution was found to be stable. CGA 64250 represented more than 98% of the radioactivity in the application solution.

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TABLE 2. Formulation of [phenyl-U-^{14}C] CGA 64250 for the *in vivo* and *in vitro* rat and human percutaneous penetration experiments (MRID 46250702 & 46250701).				
Exp. Group	**[^{14}C] CGA 64250 (mg)**	**non-labeled CGA 64250 (mg)**	**Blank formulation A-6097K (mg)**	**Comments**
Low Dose	0.9	-	2.7	Diluted with 15 ml water
Mid Dose	0.6	-	1.8	Diluted with 1 ml water
High Dose	7	493	1500	

Data taken from p. 19 of MRID 46250702 & MRID 46250701.

Application: In MRID 462507012, 100 µL was applied and spread evenly using a syringe across 10 cm^2 of the enclosed skin surface inside an 'O'-ring. The dosing site was covered with a permeable tape (non-occlusive conditions). Ingestion of the test substance was prevented by a collar around the rat's neck. Treated animals were placed in Plexiglass metabolism cages equipped with urine and feces collection. CO_2 was not collected. Anesthesia was induced using isoflurane (5% v/v) and maintained at 1.5% during dermal application and removal of the unabsorbed dose.

In MRID 46250701, the *in vitro* dermal penetration study, a 6:1 aliquot of the dosing suspension was pipetted to a dermal membrane test cell. The applied dose was verified by determining the radioactivity in three control doses.

Quantification: The purity of the formulated test substance at the time of application was checked by thin layer chromatography. Radioactivity (dpm) and homogeneity of the doses were not determined before or after dosing.

4. **Skin Wash** In MRID 46250702, the protective cover was removed (retained for analysis) at 6 hours and the application site washed at least five times with a mild soap solution (0.04%, pH 5.0) and cotton swabs. The skin was dried with cotton swabs and a fresh cover applied to the 'O'-ring.

5. Sample Collection

All specimens were individually and separately collected and all volumes or weights were recorded in the *in vivo study* (MRID 46250702). All collected specimens were kept at ambient temperature except where noted until analysis.

Urine and feces were collected at 0-6, 6-24 and 24-36 hour intervals after skin application. The collection urine vessels were surrounded by solid carbon dioxide and transferred to storage vessels afterwards and kept frozen. Feces was collected at ambient temperature, but were stored frozen.

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Blood was taken from each animal of the 48 hour subgroup. At 0.5, 1, 2, 4, 6, 8, 24, and 48 hour after exposure. Serial blood specimens were taken from the tail vein (vein sacralis media) by cutting the tip of the tail. Blood specimens were analyzed immediately after collection. The animals were sacrificed at the end of each exposure time by exsanguation after anesthesia with carbon dioxide in a desiccator. Terminal blood from each animal was collected in heparnized tubes. Aliquots of whole blood were analyzed immediately. Plasma was separated from the whole blood samples and was kept frozen until analysis.

Skin: Upon sacrifice, the treated skin was removed from the rat and retained for analysis. A small piece of non-treated skin was excised from the shaved area away from the application site. The residual carcasses were retained frozen.

Skin/membrane wash (application site): The skin washes at 6 hrs and all swabs were collected and extracted with 50 mL methanol.

Apparatus. After sacrifice at prescribed times, the used cover plates and the 'O'-rings were combined and extracted 2 times with about 80 mL methanol each at ambient temperature.

Cage Wash. At the end of the collection period, the cages were rinsed thoroughly with water/ethanol (1:1 v/v). The cage wash was kept at ambient temperature until analysis.

In the *in vitro* dermal penetration study ((MRID 46250701), at the end of exposure the dermal epidermal surface was rinsed with ethanol/water (1:1 v/v) and the radioactivity in the skin rinse was determined by LSC. The epidermal membrane was removed from the in-line cells and retained for radiometry. The cells were finally washed with ethanol/water (1:1 v/v) and the radioactivity in the cell wash was determined by LSC.

6. Sample Preparation and Analysis

Specimen Analysis

Liquid Specimens: Aliquots of liquid specimens, i.e. diluted dose solutions (0.025-0.100 mL), urine (0.05-0.2 mL), cage wash (1-2 mL), skin wash (0.025-1.0 mL), 'O'-ring and cover extract (2 mL) and plasma (0.2-0.3 g) were added directly to scintillation mixture for radioactivity measurement.

Solid Specimens: Feces were homogenized in water and 0.25-0.3 g aliquots were combusted for radioactivity analysis. Aliquots of homogenized carcass (0.25-0.30 g), and whole blood (serial blood: 0.040-0.096, terminal blood: 0.24-0.27 g) were combusted in a Packard sample oxidizer. The radioactivity in the treated and untreated skin was determined after digestion in a tissue solubilizer. The digested specimens were neutralized with hydrochloric acid and mixed with scintillation liquid prior to LSC.

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Liquid Scintillation Counting: Radioactivity was measured in a Packard Tri-Carb scintillation counter (2000CA) equipped for computing quench-corrected dpm's. Radioactivity in samples was corrected for background by subtraction appropriate blanks values.

Thin layer chromatography (TLC): Pre-coated silica gel plates (60 F_{254}; 20 x 20 cm. 0.25 mm) were used in conjunction with two solvent systems (CRM1: ethyl acetate and CRM2: chloroform/toluene/ethanol: 75/20/5, v/v/v). Non-radioactive components were visualized under UV light. Aliquots of the skin wash (25-100 uL) from each animal were analyzed by TLC to investigate the stability of the test substance over the exposure period. Radioactivity on the TLC plates was detected using a Packard instant imager or bio-imaging analyzer and the quantification of radioactive zones was performed on the instant imager software or TINA software..

Radioanalysis procedures were not validated by (e.g., analyzing control feces, blood, carcass, skin and urine samples that fortified with known amounts of the radiolabeled active ingredient). Analytical recoveries were not reported. Limits of detection (L_D) and limits of quantification (L_Q) were calculated. Recovery tests for the sample oxidizer were performed at the beginning of each day and with each combustion sequence of 20 specimens. Combustion and trapping efficiencies were above 95% and reported data were therefore not corrected. Radioactivity counts of specimens were corrected for background using appropriate blanks.

Total amounts of radioactivity in samples were reported as a percentage of the total dose.

7. **Statistics/Calculations.** Statistics was limited to computation of the mean and standard deviation where appropriate. Most calculations in the *in vivo* study were based on duplicate measurements except blood kinetics data were based on single aliquot measurement. In the *in vitro* study all data were based on single measurements. Net dpm per sample was determined by subtracting background dpm of appropriate blanks from the specimen dpm counts.

In the *in vitro* absorption study, the penetration over a specific time period P_t was calculated as:

$$P_t = \frac{RA}{t \times SA \times AE}$$

where: t = time interval (min)
SA = sp. activity (Bq/µg)
AE = exposed area of epidermal membrane (0.64 cm^2)

Cumulative penetration was determined as the summation of P_t over the 0-48 hr time period. **Absorption (penetration) rate** , or flux (J. expressed as µg/cm^2/hr) was calculated as the slope of the regression line for cumulative penetration vs time during steady-state conditions.

The permeability coefficient (K_p) was determined as the quotient of the flux constant (J) and the applied dose (c).

II. RESULTS

A. SIGNS AND SYMPTOMS OF TOXICITY

Some animals exhibited signs of stress (chromodacyorrhoea) and all animals exhibited weight loss.

B. DISPOSITION OF RADIOACTIVITY

Recovery of administered radioactivity ranged from 95% to nearly 100% in the *in vivo* study (Table 3).

TABLE 3. Radioactivity inventory (% of dose administered) for rats Following dermal application of [phenyl-U-^{14}C] CGA 64250 (formulated propiconazole)[1]

Dose Group	Low dose 0.6 ug/cm^2			Mid dose 6 ug/cm^2			High dose 2327 ug/cm^2		
Subgroup	6 hrs	24 hrs	48 hrs	6 hrs	24 hrs	48 hrs	6 hrs	24 hrs	48 hrs
Urine									
0-6 hrs	0.78	1.03	1.70	1.45	2.17	2.31	0.35	0.31	0.48
6-24 hrs	-	4.73	5.13	-	7.54	6.44	-	1.44	1.65
24-48 hrs	-	-	1.57	-	-	1.51	-	-	0.53
Feces									
0-6 hrs	0.07	0.01	0.07	0.07	0.03	0.16	0.01	<0.01	<0.01
6-24 hrs	-	6.71	5.76	-	9.81	7.36	-	2.10	1.98
24-48 hrs	-	-	1.6	-	-	1.80	-	-	0.49
Cage wash	0.23	0.61	0.89	0.39	0.63	0.82	0.05	0.30	0.24
Total Excretion	1.08	13.08	16.72	1.90	20.17	20.39	0.41	4.17	5.37
Residues									
Whole blood	0.05	<0.01	<0.01	0.18	0.02	<0.01	0.03	<0.01	<0.01
Non-treated skin	0.03	<0.01	<0.01	0.02	<0.01	<0.01	<0.01	<0.01	<0.01
Carcass	11.25	0.82	<0.01	14.79	2.53	0.59	6.38	0.59	0.22
Absorbed	12.41	13.90	16.72	16.89	22.73	21.00	6.83	4.76	5.59
Treated skin	10.29	8.16	7.66	9.37	5.92	5.63	3.56	1.56	1.81
Dislodged dose	75.14	72.98	70.88	70.51	69.95	70.31	88.49	93.42	91.50
Total recovery	97.84	95.05	95.26	96.77	98.60	96.94	98.89	99.74	98.90

Data taken from p. 30 and Tables 7-15, pp. 39-47, MRID 46250702.
[1]mean of 4 animals/group

For the *in vitro* study, percutaneous penetration was notably greater for rat epidermis (89.93, 96.02% and 69.82% of applied low- , mid- and high-dose, respectively) than for human epidermis (25.61%, 15.08% and 13.83% for low-, mid- and high-dose, respectively) as seen in Table 4. For both the rat and human epidermal membranes, exposure at the high dose resulted in a decrease in the per cent of applied dose that penetrated the epidermal membranes. Significant

amounts of radioactivity were recovered in the skin rinse, and epidermis, especially for the high-dose applications. Total recovered radioactivity was acceptable and ranged from 101% to 114% of the applied dose.

TABLE 4. Recovery of radioactivity (% dose) following application of [phenyl-U-^{14}C] CGA 64250 to rat or human epidermal membranes

Test system	Rat epidermis (Q1)			Human epidermis (Q2)		
Dose level	A1	A2	A3	A1	A2	A3
Applied dose (:g/cm^2)	0.56	5.2	2142	0.56	5.2	2166
Perfusate (0-48 hours)	89.83*	96.02	69.82	25.61	15.08	13.83
Remaining dose						
Cell wash	9.91	0.36	12.17	2.40	2.23	11.03
Skin wash	11.52	3.81	12.88	73.46	75.91	57.52
Epidermis	3.06	1.05	9.65	7.61	8.49	20.94
Subtotal	24.49	5.21	34.69	83.47	8.62	89.48
Recovery	114.32	101.23	104.51	109.08	101.71	103.32

* Group Q1A1 was prematurely terminated (26 hours after start of exposure.
Data taken from p. 28 of MRID 46250701

C. TOTAL ABSORBED DOSE

Estimates of dermal absorption were based on the sum of residues in the urine (including cage wash and rinse) + feces + carcass + blood. The bulk of absorbed radioactivity occurred during the first 6 hours, with continued absorption during the 24 and 48 hour exposure intervals at the low and the mid dose after washing the treatment site, but not at the high dose. The low absorption at the high dose (4.76%-6.83%) suggests saturated absorption at this dose. The dislodged dose removed by washing the treatment site after 6 hours exposure was highest at the high dose. The absorbed radioactivity was excreted nearly equally in the urine and feces. An insignificant amount of radioactivity was detected in the carcass after 48 hours of exposure in all of the doses, suggesting complete excretion. Residual radioactivity in the treated site decreased slowly over time.

The absorbed amounts of radioactivity per cm^2 were computed in the study report. These were 0.074, 0.083 and 0.100 ug/cm^2 for the low dose; 1.01, 1.36, and 1.26 ug/cm^2 for the mid dose and 159, 111, and 130 ug/cm^2 for the high dose at 6, 24, and 48 hour intervals, respectively. The penetration rate for the exposure period of 6 hours was calculated to be 0.012, 1.69, 26.5 ug/cm^2 /hr at the low, mid and high doses, respectively.

Blood levels in the low dose group were below the limit of detection. Blood levels in the mid and dose groups peaked at 6 hours of exposure coinciding with the exposure duration and declined to non detectable afterwards. Terminal residues for various compartments are shown in Table 5.

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TABLE 5. Terminal Residues (ppm eq.) Following dermal application of [phenyl-U-^{14}C] CGA 64250 to rats									
Group	Low dose 0.6 ug/cm^2			Mid dose 6 ug/cm^2			High dose 2327 ug/cm^2		
Sacrifice	6 hr	24 hr	48 hr	6 hr	24 hr	48 hr	6 hr	24 hr	48 hr
Blood	<LQ	<LD	<LD	0.011	0.001	=LQ	0.843	0.091	<LQ
Plasma	0.0014	=LD	<LD	0.020	0.003	0.001	1.515	0.166	0.087
Skin, non-treated	0.0010	=LD	<LD	0.010	0.002	0.001	1.127	0.076	0.060
Carcass	0.0029	<LQ	<LD	0.041	0.007	0.002	7.121	0.602	0.221

Data taken from p. 32 of MRID 46250702

C. **PHARMACOKINETICS**: Time-course data for blood samples from rats in mid- and high-dose 48 hour subgroups revealed that radioactivity in the blood increased rapidly with a T_{max} of 2 to 6 hours (Table 6). In the low dose groups blood residues were non-detectable.

TABLE 6. Time-course data (expressed as CGA 64250 ppm eq.) for blood radioactivity in rats following dermal application of [phenyl-U-^{14}C] CGA 64250 (Propiconazole)[a]			
Time (hrs)	Low dose	Mid dose	High dose
0.5	<LD	0.0028	<LQ
1	<LD	0.0072	0.3397
2	<LD	0.0103	0.6179
4	<LD	0.0082	0.6595
6	<LD	0.0088	0.8278
8	<LD	0.0066	0.6084
24	<LD	<LQ	<LD
48	<LD	<LQ	<LD

Data taken from p. 38, Tables 4-6 of MRID 46250702

Selected time-course data and flux rates for the human and rat epidermal membrane preparations in the dermal penetration study (MRID 46250701) are shown in Table 7. Significant differences were observed between dose groups and between the human and rat epidermis preparations. Cumulative penetration as percent of applied dose was notably lower in the high-dose group and for the human relative to rat epidermal preparations. Flux was considerably greater (95-fold for the low dose, 17-fold for the mid dose and 11-fold for the high dose) for the rat epidermal preparation compared to human dermal preparation (Table 7).

TABLE 7. Selected cumulative time-course data[a] and flux rates for dermal penetration of [phenyl-U-^{14}C] CGA 64250 (Propiconazole) through rat and human epidermis.						
Time (hrs)	Rat			Human		
	Low dose	Mid dose	High dose	Low dose	Mid dose	High dose
2	42.13±13.69	94.91±17.9	7.25±4.23	7.43±8.51	4.12±4.41	0.06±0.07
4	71.38±13.31	77.32±11.86	14.91±8.32	9.92±11.82	4.56±4.82	0.47±0.37
8	81.12±10.40	84.16±8.62	27.49±12.47	12.33±13.15	5.35±5.46	1.12±0.67
12	85.18±8.94	89.08±5.42	36.65±14.18	14.17±13.74	6.21±6.09	2.21±1.02
24	89.47±7.40	94.05±3.66	54.46±13.18	18.59±14.47	8.82±7.90	5.88±2.04
48	-	96.02±2.62	69.82±10.86	25.61±16.98	15.08±11.71	13.83±3.83
Flux (ug/cm^2/hr)[b]	1.81±0.061	1.994±1.201	76.2±42.1	0.019±0.021	0.107±0.115	6.988±1.719

[a] Expressed as per cent of applied dose.
[b] Flux was calculated as the slope of the regression line for cumulative penetration vs time during steady-state conditions.
Data taken from Tables 3-14, pp. 35-46 and Table 9, p. 37, MRID 46250701.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that dermal exposure of rats for 6 hours to [phenyl-U-^{14}C] CGA 64250 resulted in moderate absorption of 12, 17 and 7% of the applied dose at 0.6, 6 or 2327 ug/cm^2 application doses, respectively. The calculated penetration rates during the 6 hour exposure time were 0.012, 1.69, 26.5 ug/cm^2 /hr at the low, mid and high doses, respectively. The nearly 4000 fold higher concentration at the high dose level led only to 2000 fold higher penetration rate as compared to the low dose level. The majority of the applied dose was washed off after the 6 hours exposure time. Only 10%, 9% and 4% of the dose remained in/on the treated skin site for the low, mid and high dose, respectively. The remaining radioactivity at the treated site resulted in slight increase of the systemic absorption at the low- and mid- dose levels accounting for 17 and 21% of the applied dose, respectively. At the high dose level, the systemic absorption remained constant within 42 hours after washing the treated skin site. The absorbed radioactivity was equally distributed between the urine and the feces. The residues in the carcass were attributed to non excreted feces.

In the *in vitro* epidermal penetration study (MRID 46250701) [phenyl-U-^{14}C] CGA 64250 (formulated as TILT^{R}250 EC), exhibited both dose and species variability in penetration through epidermal membrane preparations. The investigators concluded that percutaneous absorption of the test article over the 48-hour experimental period was notably less for human epidermal preparations than for rat epidermal preparations. At steady state conditions, flux was considerably greater (95-fold for the low dose, 17-fold for the mid dose and 11-fold for the high dose) for the rat epidermal preparation compared to human dermal preparation.

B. REVIEWER COMMENTS: The EPA reviewers agree with the findings of the study that CGA 64250 is moderately absorbed after 6 hours by the rat skin. Retained radioactivity in the skin site after it has been washed after 6 hour exposure provided a source of additional slow systemic absorption. Thus the absorbed radioactivity increased from 12% and 17% at 6 hours to 17% and 21% at the 48 hour sacrifice time for the low and mid doses, respectively. This demonstrates that if the exposure period to the test substance was longer, the extent of the systemic absorption would also be higher. From the calculated penetration rates in this study systemic absorption at longer exposures can be computed.

This study was conducted at test concentrations (low and mid dose) to reflect typical concentrations recommended in the field. The exposure time of 6 hours was chosen to reflect the OECD guidelines based on anticipated exposure period of a plant and field worker. However, this exposure period does not meet the EPA guidelines of using several exposure periods including a 10 hour duration, where such duration is used to derive an absorption rate for a typical work day in the USA. Therefore this study (MRID 46250702) although scientifically acceptable, it does not meet the EPA guideline OPPTS 870.7600 for a dermal penetration study and is considered **Acceptable/Non-Guideline**. However, the findings in this study are consistent with results obtained from an **Acceptable/Guideline** Study (MRID 00164469) where absorbed dose at 2 and 4 hour exposures was within the range of the absorbed dose after 6 hours exposure in the current study. A longer exposure duration to 10 hours in MRID 00164469 study resulted in higher absorption indicating that in the current study under review if exposure duration was extended to 10 hours absorbed values would be comparable to the MRID 00164469 study.

The percutaneous absorption study (MRID 46250701) utilized epidermal membranes prepared from rat and human (cadaver) abdominal skin to which was applied [phenyl-U-^{14}C] CGA 64250 (formulated as TILT®250 EC). Percutaneous absorption was assessed over 48 hours. The data support the study author's conclusions. Under the conditions of this study, species variability (rat vs human) in the percutaneous absorption of CGA 64250 is clearly indicated. The transfer of test article across the epidermal membranes was notably greater for the rat epidermal preparation than for the human epidermal preparation; flux values were considerably greater (95-fold for the low dose, 17-fold for the mid dose and 11-fold for the high dose) for the rat epidermal preparation compared to human dermal preparation. In comparing the different doses, flux increased proportionally with increased dose for rat and human skin. Flux was 1.81, 1.994, 76.2 ug/cm^2/hr for the rat, and 0.019, 0.107, 6.988 ug/cm^2/hr for the human skin at the low-, mid- and high-dose, respectively resulting in greater absolute amounts of test article being transferred across the epidermal membranes at the high dose but resulting in a decrease in percutaneous absorption expressed as per cent of applied dose. It is apparent that percutaneous absorption at the high application level represented saturation.

C. STUDY DEFICIENCIES: The study was conducted only at one exposure of 6 hour duration. It should include other exposure durations such as 0.5, 1, 2, 4, 10, and 24 hours.

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