323EE

CASWELL FILE

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

010242

JAN 1 3 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: Propiconazole - Review of dermal absorption study.

EPA IDENTIFICATION NUMBERS: Caswell No.: 323EE
P.C. Code: 122101
DP Barcode: D181342

FROM: Robert F. Fricke, Ph.D. Robert F. Fricke 12 Jan 93
Toxicology Branch II, Section IV
Health Effects Division (H7509C)

TO: Bruce Sidwell
Product Manager (53)
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THRU: Elizabeth Doyle, Ph.D. E.A. Doyle 1/12/93
Toxicology Branch II, Head Section IV
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia Gemert 1/13/93
Chief, Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Ciba-Geigy Corp.

Chemical: Propiconazole

Action Requested: The registrant, Ciba-Geigy Corp, has requested a review of the submitted dermal absorption study.

Dermal Absorption of $^{14}$C-Propiconazole: Addendum to ABR-86053, MRID NO.: 424157-01

Results: Male, Harlan Sprague-Dawley rats were exposed to $^{14}$C-test compound at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1 or 1 mg/cm$^2$, respectively). One group of four rats were exposed for 24 hours, while two other groups of four rats each were exposed for 10 or 24 hours followed by a 72-hour depletion phase. Following the exposure period, most of the test compound remained on the skin and was removed during the soap rinse. The amount of

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test compound absorbed was directly proportional to the applied dose. The rate of absorption appeared to be saturated at the highest dose level; at the low dose level, there was a time-dependent increase in the amount of compound absorbed. After 24 hours, 57.1, 271 and 3010 $\mu g/cm^2$ (57.13, 27.14 and 30.10 % of total dose, respectively) were absorbed at the low, mid and high dose levels, respectively. During the 72-hour depletion phase essentially all of the compound was eliminated in the urine and feces; urinary elimination predominated at the mid and high dose levels. At the end of the 72 hour depletion phase, less than 2% of the test compound was still present in the carcass.

CLASSIFICATION: core - acceptable

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 12 Jan 93
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D. E.A. Doyle 1/12/93
Section IV, Tox. Branch II (H7509C)

**DATA EVALUATION REPORT**

010242

**STUDY TYPE:** Dermal absorption in rats (85-2)

**P.C. CODE:** 122101 **CASWELL NO.:** 323EE

**MRID NO.:** 424157-01

**TEST MATERIAL:** CGA-64250, Propiconazole

**SYNONYMS:** 1-[[2-(2',4'-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]-methyl]-1H-1,2,4-triazole

**STUDY NUMBER:** ABR-86064

**SPONSOR:** Agricultural Division
CIBA-GEIGY Corporation
P.O. Box 18300
Greensboro, NC 27419

**TESTING FACILITY:** Agricultural Division
CIBA-GEIGY Corporation
P.O. Box 18300
Greensboro, NC 27419

**TITLE OF REPORT:** Dermal Absorption of $^{14}$C-Propiconazole: Addendum to ABR-86053

**AUTHOR:** T. Murphy

**REPORT ISSUED:** 30 September 1986

**CONCLUSIONS:** Male, Harlan Sprague-Dawley rats were exposed to $^{14}$C-test compound at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1 or 1 mg/cm$^2$, respectively). One group of four rats were exposed for 24 hours, while two other groups of four rats each were exposed for 10 or 24 hours followed by a 72-hour depletion phase. Following the exposure period, most of the test compound remained on the skin and was removed during the soap rinse. The amount of test compound absorbed was directly proportional to the applied dose. The rate of absorption appeared to be saturated at the highest dose level; at the low dose level, there was a time-dependent increase in the amount of compound absorbed. After 24 hours, 57.1, 271 and 3010 $\mu$g/cm$^2$ (57.13, 27.14 and 30.10 % of total dose, respectively) were absorbed at the low, mid and high dose levels, respectively. During the 72-hour depletion phase essentially all of the compound was eliminated in the urine and feces; urinary elimination predominated at the mid and high dose levels. At the end of the 72 hour depletion phase, less than 2% of the test compound was still present in the carcass.

**CLASSIFICATION:** core - acceptable 3

## I. MATERIALS AND METHODS

A. Test compound: Triazole-[3,5-$^{14}$C]-CGA-64250, Lot No.: not given, Radiochemical purity: 95%, Specific Activity: 28.2 μCi/mg (low and mid dose levels) and 2.01 μCi/mg (high dose level). Dermal application of the test compound was made at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1, or 1.0 mg/cm$^2$, respectively). The radioactive test compound was added to the 3.6EC formulated product (45.8% active ingredient and 54.2% inert substances) and applied as an aqueous suspension.

B. Test animals: Male, Harlan Sprague-Dawley rats (Madison, WI) with mean bodyweight range was 200-250 g were used in this study. The age of the animals was not given.

C. Study Design: Animals were allocated to study and dose groups as shown in Table 1. Approximately 24 hours before exposure, the dorsal hair was shaved and the skin cleaned with acetone. Test compound was applied to a 10 cm$^2$ area (4.0 cm x 2.5 cm) at dose volumes 50 μl (Groups I and II) or 100 μl (Group III). Test compound was spread evenly over the marked application site, allowed to air dry for approximately 5 to 10 min, and then covered with a non-occlusive dressing. The dressing consisted of Stomahesive (Squibb Corporation), filter paper and an aluminum bridge. Animals were housed in separate metabolic cages and allowed free access to both food and water.

Table 1: Study Design

| Group | Time (hr) Exposure | Time (hr) Depletion | Dose (mg/rat) | No. of Animals |
|---|---|---|---|---|
| I | 24 | 0 | 0.1 | 4 |
| | | | 1.0 | 4 |
| | | | 10 | 4 |
| II | 10 | 72 | 0.1 | 4 |
| | | | 1.0 | 4 |
| | | | 10 | 4 |
| III | 24 | 72 | 0.1 | 4 |
| | | | 1.0 | 4 |
| | | | 10 | 4 |

At the end of the exposure period, the dressing was removed. Using sterile gauze pads, the skin was washed twice with soapy water and rinsed with deionized water. The combined soap rinses and water rinse were collected and brought to a final volume of 100 ml. Components of the

non-occlusive dressing were separated and washed individually in methanol. Fecal and urinary samples were collected at the end of the exposure periods (10 or 24 hr) and at 24 hour intervals following the exposure.

After the animals were euthanized, samples of treated (Skin I) and untreated (Skin II, unexposed skin under the patch) skin were collected, solubilized, digested and radioassayed. Aliquots of the urine, skin rinses, dressing rinses and cage washes were radioassayed directly. Pooled fecal samples and the carcass were ground and homogenized. Feces, carcass, blood, gauze pads (from skin rinses), and filter paper (from dressing) were combusted and radioactivity determined.

D. Statistics: Statistical data were based on radioactive counting with a detection limit for quantitation set at twice the background rate.

E. Quality Assurance: Quality assurance was documented by signed and dated GLP and quality assurance statements.

F. Flagging Statement: Not present

II. Results: The results presented in this study are an addendum to a previously submitted study (MRID 265795). While the previous study measured the absorption following a 2-, 4- or 10-hour exposure to test compound, the present study examined results of a 24-hour exposure and a 10- or 24-hour exposure with a 72-hour depletion phase. The results are summarized in Appendix 1. The radioactivity present in excreta, blood, carcass, skin, skin washes and patch components were determined. The applied radioactivity was accounted for, with recoveries ranging from 82.8 to 108 %.

The urinary and fecal elimination of test compound was measured at 24-hour intervals following the exposure period (Table 2). At the low dose urinary and fecal elimination were comparable. As the dose increased, urinary elimination become predominant route of elimination.

Even though the percentage of test compound absorbed decreased with increasing dose, absorption, expressed as $\mu g/cm^2$, indicated that the actual amount absorbed is directly proportional to the applied dose (Table 3).

For completeness, the absorption data presented in the main study and Amendment I of the study were summarized (Table 3). At the 0.1 mg/rat dose there was a time-dependent increase in the amount of compound absorbed. At both 1.0 and 10 mg/rat doses, saturation was evident as early as 2 hours after exposure.

5

Table 2: Urinary and Fecal Elimination Following a 10- or 24-Hour Exposure to Test Compound[a]

| Collection Time (hr) | Amount Excreted (μg) at Doses (mg/rat) of 0.1 Urine | 0.1 Feces | 1.0 Urine | 1.0 Feces | 10 Urine | 10 Feces |
|---|---|---|---|---|---|---|
| 10-Hour Exposure | | | | | | |
| 10 | 5.13 | 0.19 | 19.3 | 0.5 | 84 | 2 |
| 34 | 11.11 | 13.46 | 68.1 | 53.2 | 798 | 360 |
| 58 | 3.81 | 3.96 | 27.3 | 19.4 | 636 | 518 |
| 82 | 1.56 | 1.62 | 10.2 | 7.7 | 265 | 248 |
| Total | 20.05 | 19.23 | 114.7 | 80.8 | 1518 | 1128 |
| 24-Hour Exposure | | | | | | |
| 24 | 16.96 | 11.94 | 63.8 | 26.6 | 700 | 110 |
| 48 | 6.96 | 9.41 | 63.8 | 60.0 | 660 | 374 |
| 72 | 3.74 | 2.23 | 21.6 | 22.9 | 404 | 308 |
| 96 | 1.08 | 0.91 | 12.2 | 12.1 | 154 | 105 |
| Total | 28.74 | 24.49 | 161.4 | 121.6 | 1918 | 897 |

[a] Amount of compound excreted was calculated from the data presented in study Tables II and III.

Table 3: Dermal Absorption[a] of Test Compound at Doses 0.1, 1.0 and 10 mg/rat (Data calculated from study results)

| Group | Time (hr) Exposure | Depletion | Absorption (μg/cm$^2$) at 0.1 | 1.0 | 10 |
|---|---|---|---|---|---|
| I | 24 | 0 | 57.1 | 271 | 3010 |
| II | 10 | 72 | 48.3 | 252 | 3700 |
| III | 24 | 72 | 59.4 | 354 | 4240 |

[a] Absorption = Dose × Percent Absorbed

Table 4: Absorption of Test Compound at Doses of 0.1, 1.0 and 10 mg/rat[a]

| Exposure Time (hr) | Absorption (μg/cm$^2$) at 0.1 | 1.0 | 10 |
|---|---|---|---|
| 2 | 34.7 | 262 | 3010 |
| 4 | 49.5 | 361 | 3107 |
| 10 | 53.7 | 362 | 2929 |
| 24 | 57.1 | 271 | 3010 |

[a] 24-hour data calculated from study results, Table I; 2-, 4-, and 10-hour data were calculated from results presented in Amendment I of the study (Appendix 2 this review).

III. Discussion: Male, Harlan Sprague-Dawley rats were exposed to $^{14}C$-test compound at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1 or 1 mg/cm$^2$, respectively). One group of four rats were exposed for 24 hours, while two other groups of four rats each were exposed for 10 or 24 hours followed by a 72-hour depletion phase. Following the exposure period, most of the test compound remained on the skin and was removed during the soap rinse. The amount of test compound absorbed was directly proportional to the applied dose. The rate of absorption appeared to be saturated at the highest dose level; at the low dose level, there was a time-dependent increase in the amount of compound absorbed. After 24 hours, 57.1, 271 and 3010 $\mu$g/cm$^2$ (57.13, 27.14 and 30.10 % of total dose, respectively) were absorbed at the low, mid and high dose levels, respectively. During the 72-hour depletion phase essentially all of the compound was eliminated in the urine and feces; urinary elimination predominated at the mid and high dose levels. At the end of the 72 hour depletion phase, less than 2% of the test compound was still present in the carcass.

Classification: core - Acceptable

RIN 1067-98

Propiconazole (Tilt) Tox Review

Page_____ is not included in this copy.

Pages 8 through 14 are not included.

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