13544

010547

Chemical:	**Propiconazole**
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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

011833

CASWELL FILE

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

MAR - 7 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PROPICONAZOLE** - Review of acute toxicity studies with Tilt 45WP to support "F" petition for tolerance in/on bloom-only applications to cherries and all crops with existing propiconazole tolerances.

EPA IDENTIFICATION NOs.: Caswell No.: 323EE
P.C. Code: 122101
DP Barcode: D217197
Submission No.: S489753
Petition No.: 4F04321 (Amended 15 May 1995)

FROM: Robert F. Fricke, Ph.D. Robert F. Fricke 29 Feb 96
Toxicology Branch II, Section II
Health Effects Division (7509C)

TO: Connie Welch/Kathyrn Scanlon
Product Manager (21)
Registration Division (7505C)

THRU: K. Clark Swentzel K. Clark Swentzel 2/29/96
Toxicology Branch II, Head Section II
Health Effects Division (7509C)

and

Stephanie Irene, Ph.D.
Acting Chief, Toxicology Branch II
Health Effects Division (7509C) Stephanie R. Irene 3/7/96

REGISTRANT: Ciba-Geigy Corp

CHEMICAL: Propiconazole, Technical (88% a.i.)
CGA64250 45WP, Tilt 45WP (46.4% a.i.)

ACTION REQUESTED: Review acute toxicity studies with Tilt 45 WP to support the Registrant's petition (4F04321, amended 15 May 1995) to establish a tolerance for bloom-only application to cherries. The Registrant also requests the registration of Tilt 45WP formulation of propiconazole for use on **all crops** with propiconazole tolerances.

BACKGROUND: A tolerance of 1.0 ppm for propiconazole (§180-434) has been approved for selected stone fruits (apricots, nectarines, peaches, plums and fresh prunes). The Registrant has submitted an amendment to Petition No. 4F04321 and necessary acute toxicity studies to support establishment of a tolerance for Tilt 45WP for bloom-only application to sweet and sour cherries and for registration of Tilt 45WP formulation of propiconazole for use on all crops with propiconazole tolerances.

SUMMARIES OF ACUTE TOXICITY STUDIES WITH TILT 45 WP

1. Acute Oral Toxicity Study in Rats (§81-1): J.O. Kuhn (20 April 1995) Acute Oral Toxicity Study in Rats, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1855-95, MRID No.: 43655603, unpublished

In this acute oral toxicity study, male and female Sprague-Dawley rats (5/sex) were orally gavaged with an aqueous suspension (40% (w/v) of test compound to produce dose levels of 500, 1000/1250 (males/females), 2000, 3000 or 5050 mg/kg. Clinical signs observed during the day of dosing included a high incidence of piloerection and decreased activity at all dose levels; ptosis was observed at 1000/1250 mg/kg and higher doses, and salivation at 2000 mg/kg (males only) and higher. Clinical signs were most prevalent on Day 0 with decreasing incidence on succeeding days. Deaths were observed from Day 1 to 2 at 5050 mg/kg and Day 1 to 3 at lower doses.

LD_{50}: 2510 mg/kg (males), 1161 mg/kg (females), 1587 mg/kg (combined)
Toxicity Category III
Classification: ACCEPTABLE

2. Acute Dermal Toxicity Study in Rabbits: J.O. Kuhn (18 April 1995) Acute Dermal Toxicity Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1856-95, MRID No.: 43655604, unpublished

In this acute dermal toxicity study, a single dose (2020 mg/kg) of moistened test material was applied to the clipped, intact dorsal skin of rabbits (5/sex) on Day 0. Application sites were covered with an occlusive dressing during the 24-hour exposure period. All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Body weights and body weight gains were, in general, unaffected by treatment. At terminal sacrifice (Day 14) no abnormalities were noted during the gross examination.

LD_{50}: > 2020 mg/kg (males and females)
Toxicity Category III
Classification: ACCEPTABLE

3. Acute Inhalation Toxicity Study in Rats: J.O. Kuhn (20 April 1995) Acute Inhalation Toxicity Study in Rats, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1868-95, MRID No.: 43655605, unpublished

Sprague-Dawley rats (5/sex/dose) were exposed to powder aerosols at concentrations of 1.69 and 5.54 mg/L for four hours and observed daily for 14 days. All animals survived to terminal sacrifice. Piloerection, decreased activity, ptosis and fur coated with feces and urine were observed in all animals for approximately four days post exposure. Animals were generally free of clinical signs by Day 4 or 5. Average MMAD values were 2.872 μm (1.69 mg/L) and 8.172 μm (5.54(mg/L). The total mass of particles having diameters of 1 μm and less was calculated to be 13.5% for both 1.69 mg/L and 5.54 mg/L, and diameters of 5 μm and less, 71.5% at 1.69 mg/L and 54% at 5.54 mg/L.

LC_{50} > 5.54 mg/L for males and females
Toxicity category IV
Classification: ACCEPTABLE

4. Primary Eye Irritation Study in the Rabbit: J.O. Kuhn (4 May 1994) Primary Eye Irritation Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1072-94, MRID No.: 43655606, unpublished

The eye irritation potential of the test compound (0.1 mL, 23.6 mg) was evaluated in non-washed and washed (30 sec post-dosing with deionized water) eyes of NZW rabbits. Animals (3/sex) with non-washed eyes had corneal opacity and chemosis through 48 hours post-dosing, and conjunctival redness through 72 hours; no iritis was noted. Eyes were completely cleared by Day 7. For washed eyes, the only signs of eye irritation were conjunctival redness and chemosis noted at 1 hour post dosing.

Toxicity category III (moderate eye irritation)
Classification: ACCEPTABLE

5. Primary Dermal Irritation Study in the Rabbit: J.O. Kuhn (17 April 1995) Primary Dermal Irritation Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1857-95, MRID No.: 43655607, unpublished

In this dermal irritation study, test material was evaluated in NZW rabbits (3/sex). After a 4-hour exposure with 400 mg test material (moistened with deionized water), the application sites were cleaned of residual test compound and scored for edema and erythema (Draize method) within 30 min and at 24, 48 and 72 hr. After a 4-hour exposure the application sites were cleaned of residual test compound and scored. Very slight erythema (Draize Score = 1) was observed in 4/6 animals at 1/2 hr and 2/6 at 24 hr; no erythema or edema were observed at any other time points. Based on the PII value of 0.2, the test material was found to produce slight dermal irritation.

Toxicity category IV (PII = 0.2, slightly irritating)
Classification: ACCEPTABLE

6. Dermal Sensitization Study in the Guinea Pig: J.O. Kuhn (20 April 1995) Dermal Sensitization Study in Guinea Pigs, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1858-95, MRID No.: 43655608, unpublished

Buehler's method was used to evaluate the skin sensitization potential of the test material in guinea pigs. Following induction and challenge with 400 mg test material (moistened with 0.35 mL of deionized water), no dermal sensitization was noted in any of the treated animals. Naive control animals were also negative for dermal irritation, while DNCB-treated, positive control animals had a mean score of 1.8 after rechallenge.

Not a skin sensitizer
Classification: ACCEPTABLE

TOXICOLOGY PROFILES

1. Technical Grade Propiconazole (88 to 92.1%):

GUIDELINE	STUDY TYPE	REQUIRED	SATISFIED	MRID/ACCESSION NO
81-1	Acute Oral	Yes	Yes	244271, 244272
81-2	Acute Dermal	Yes	Yes	244271, 244272
81-3	Acute Inhalation	Yes	Yes	244272
81-4	Primary Eye Irritation	Yes	Yes	244271, 244272
81-5	Primary Dermal Irritation	Yes	Yes	244272
81-6	Primary Dermal Sensitization	Yes	Yes	244272
82-1(a)	90-Day Feeding (rodent)	Yes	Yes	244272
82-1(b)	90-Day Feeding (dog)	Yes	Yes	244272
82-2	21-Day Dermal (rabbit)	Yes	Yes	424157-01
83-1(a) & 83-2(b)	Chronic Feeding/ Oncogenicity (mouse)	Yes	Yes	250784, 250786, 251237, 073919
	Chronic Feeding/ Oncogenicity (rat)	Yes	Yes	250787, 250790, 073018
83-1(b)	Chronic Feeding (dog)	Yes	Yes	73928
83-3(a)	Developmental (rat)	Yes	Yes	244272, 404250-01
83-3(b)	Developmental (rabbit)	Yes	Yes	244272
83-4	Reproduction, 2 Gen (rat)	Yes	Yes	073923, 073927
84-2	Gene Mutation	Yes	Yes	244272, 072206, 073920
	Chromosomal Aberration	Yes	Yes	244272
84-4	Other Genotoxic Effects	Yes	Yes	244272
85-1	General Metabolism	Yes	Yes	265794
85-2	Metabolism, Dermal Absorption (rat)	No	Yes	265795

GUIDELINE	STUDY TYPE	REQUIRED	SATISFIED	MRID NO.
81-1	Acute Oral	Yes	Yes	436556-03
81-2	Acute Dermal	Yes	Yes	436556-04
81-3	Acute Inhalation	Yes	Yes	436556-05
81-4	Primary Eye Irritation	Yes	Yes	436556-06
81-5	Primary Dermal Irritation	Yes	Yes	436556-07
81-6	Dermal Sensitization	Yes	Yes	436556-08

RECOMMENDATION: The existing toxicology data bases for technical propiconazole and formulated end-use product Tilt 45WP are adequate, no data gaps exist which would preclude establishment of the requested tolerance for bloom-only application in cherries and all crops with existing propiconazole tolerances. Toxicology Branch II can support this action if:

a. A DRES analysis shows that the TMRC does not result in public consumption which would exceed RfD, and

b. CBTS concludes that this action does not represent a Delaney issue.

011833

y: Robert F. Fricke, Ph.D. Robert F. Fricke 27 Feb 96
x. Branch II (7509C)

ew: K. Clark Swentzel K. Clark Swentzel 2/28/96
ox. Branch II (7509C)

DATA EVALUATION RECORD

TUDY TYPE: Acute Oral Toxicity - Rats [OPPTS 870-1100, OPP 81-1]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA64250 45WP-B (46.4% Propiconazole)

SYNONYMS: TILT 45WP

CITATION: J.O. Kuhn (20 April 1995) Acute Oral Toxicity Study in Rats, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1855-95, 43655603, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: In this acute oral toxicity study (MRID No. 43655603), male and female Sprague-Dawley rats (5/sex) were orally gavaged with an aqueous suspension (40% (w/v) of test compound to produce dose levels of 500, 1000/1250 (males/females), 2000, 3000 or 5050 mg/kg. Clinical signs observed during the day of dosing included a high incidence of piloerection and decreased activity at all dose levels; ptosis was observed at 1000/1250 mg/kg and higher doses, and salivation at 2000 mg/kg (males only) and higher. Clinical signs were most prevalent on Day 0 with decreasing incidence on succeeding days. Deaths were observed from Day 1 to 2 at 5050 mg/kg and Day 1 to 3 at lower doses.

LD_{50} **2510 mg/kg (males)**
1161 mg/kg (females)
1587 mg/kg (combined)

Toxicity Category III

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-1) for an acute oral toxicity study in the rat.

MATERIALS and METHODS

Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Rat Strain: HSD: Sprague-Dawley SD; Age: 8-12 weeks; Body Weight (g): 184-264 (males), 193-238 (females); Source: Harlan Sprague-Dawley, Inc., Houston, TX; Food: Purina Formulab Chow # 5008, *ad libitum* (except 16 hr postdosing); Water: Tap water, *ad libitum;* Acclimation Period: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30-80%, Air changes: 10-12/hr, Light/dark cycle: 12hr/12 hr.

Study Design: Following an overnight fast (18 - 20 hr), male and female rats (5/sex) were orally gavaged with an aqueous suspension 40% (w/v) of test compound at dose levels of 500, 1000/1250 (males/females), 2000, 3000 or 5050 mg/kg. The dose volume was varied from 1.25 mL/kg to 12.6 mL/kg for the 500 mg/kg to 5050 mg/kg dosages, respectively. Animals were observed for signs of toxicity, moribundity and mortality during the day of dosing (Day 0) and once daily, thereafter, for 14 days. Individual body weights were recorded just prior to dosing, and on Days 7 and 14 of the observation period. At the end of the observation period animals were necropsied for gross pathological examination.

Statistics: The LD_{50} was calculated using probit analysis; no other statistical analyses were performed.

RESULTS and CONCLUSIONS

Clinical signs observed during the day of dosing included a high incidence of piloerection and decreased activity at all dose levels; ptosis was observed at 1000/1250 mg/kg and higher doses, and salivation at 2000 mg/kg (males only) and higher. Clinical signs were most prevalent on Day 0 with decreasing incidence on succeeding days. Lethality data and calculated LD_{50} values are presented in Table 1. Deaths were observed from Day 1 to 2 at 5050 mg/kg and Day 1 to 3 at lower doses.

LD_{50} 2510 mg/kg (males), 1161 mg/kg (females), 1587 mg/kg (combined)

Toxicity Category III

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-1) for an acute oral toxicity study in the rat.

TABLE 1: INDIVIDUAL MORTALITY DATA AND ESTIMATED LD_{50} VALUES (mg/kg)[a]

DOSE LEVEL		DEAD/TREATED ANIMALS		
mg/kg	mL/kg	MALES	FEMALES	COMBINED
500	1.25	0/5	0/5	0/10
1000	2.50	—	1/5	--
1250	3.13	0/5	—	—
2000	5.0	3/5	5/5	8/10
3000	7.50	3/5	5/5	8/10
5050	12.6	4/5	5/5	9/10
LD_{50} (95% Confidence Limits)		2510 (1440-4375)	1161 (932-1445)	1587 (1044 - 2414)

[a] Data summarized from page 8 of the report.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 27 Feb 96 011833
Section II, Tox. Branch II (7509C)

Secondary Review: K. Clark Swentzel K. Clark Swentzel 2/29/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation- Rabbits [OPPTS 870-2400, OPP 81-4]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA-64250 45WP-B (46.4% *Propiconizole*)

SYNONYM: TILT 45WP

CITATION: J.O. Kuhn (4 May 1994) Primary Eye Irritation Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1072-94, 43655606, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: The eye irritation potential of the test compound (0.1 mL, 23.6 mg) was evaluated in non-washed and washed (30 sec post-dosing with deionized water) eyes of NZW rabbits. Animals (3/sex) with non-washed eyes had corneal opacity and chemosis through 48 hours post-dosing, and conjunctival redness through 72 hours; no iritis was noted. Eyes were completely cleared by Day 7. For washed eyes, the only signs of eye irritation were conjunctival redness and chemosis noted at 1 hour post dosing.

Toxicity category III (moderate eye irritation)

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (81-4) for a primary eye irritation study in rabbits.

MATERIALS and METHODS

Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Rabbit Strain: New Zealand White; Age: 3-6 months; Body Weight (kg): 2.600-2.925 (males), 2.375-2.875 (females); Source: Ray Nichols Rabbitry, Lumberton, TX; Food: Purina Rabbit Chow, *ad libitum*; Water: Tap water, *ad libitum;* Acclimation: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30-80%, Air changes: 10-12/hr, Light/dark cycle: 12hr/12 hr.

Study Design: The eye irritation potential of test material was evaluated in NZW rabbits. Based on a prestudy ophthalmic examination of both eyes of each animal, those without any eye apparent defects were selected for the study. Animals were assigned to non-washed eye (3/sex) or washed eye (3 females) groups. For both groups, test material (0.1 mL, 23.6 mg) was instilled into the conjunctival sac of the right eye of each animal, the left eye was untreated and served as the control. For animals in the washed eye group, treated eyes were washed with deionized water beginning 30 sec after treatment. Treated eyes were examined and scored (Draize method) for ocular lesions at 1, 24, 48 and 72 hr, and at 7 and 14 days. The corneas of all treated eyes were examined with a fluorescein sodium ophthalmic solution at 24 hr post-exposure. Animals showing a positive fluorescein response were examined in a similar manner for each subsequent examination. Rabbits were weighed on the day of treatment and at study termination.

TABLE 1: EYE IRRITATION SCORES

RATING	MAXIMUM AVERAGE SCORE
Non-irritating	0.0-0.5
Practically Non-irritating	>0.5-2.5
Minimally Irritating	>2.5-15.0
Mildly Irritating	>15.0-25.0
Moderately Irritating	>25.0-50.0
Severely Irritating	>50.0-80.0
Extremely Irritating	>80.0-110.0

RESULTS and CONCLUSIONS

Study results are summarized in Table 2. Rabbits with non-washed eyes had corneal opacity and chemosis through 48 hours post-dosing, and conjunctival redness through 72 hours. No iritis was noted. Eyes were completely cleared by Day 7. For washed eyes conjunctival redness and chemosis were noted at 1 hour post dosing only; no signs of corneal opacity or iritis were observed.

TABLE 2: INCIDENCE OF POSITIVE OCULAR EFFECTS and EYE IRRITATION SCORES[a]

OBSERVATION		TIME AFTER TREATMENT					
		1 Hr	24 Hr	48 Hr	72 Hr	4 Days	7 Days
NON-WASHED EYES							
Cornea	Opacity	0/6	4/6	3/6	0/6	0/6	0/6
Iritis		0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae	Redness	6/6	6/6	5/6	1/6	0/6	0/6
	Chemosis	6/6	4/6	2/6	0/6	0/6	0/6
Eye Irritation Scores		11.3	19.3	7.2	4.0	1.3	0.0
WASHED EYES							
Cornea	Opacity	0/3	0/3	0/3	0/3	0/3	0/3
Iritis		0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae	Redness	2/3	0/3	0/3	0/3	0/3	0/3
	Chemosis	2/3	0/3	0/3	0/3	0/3	0/3
Eye Irritation Scores		10.0	4.0	2.7	0.0	0.0	0.0

[a] Data summarized from text table (pg 6) and Table 2 (pg 19).of the study.

Toxicity category III (moderate eye irritation)

This study is classified as **ACCEPTABLE** and satisfied guideline requirements (§81-4) for an eye irritation study in the rabbit.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 6 Mar 96
Section II, Tox. Branch II (7509C)

011833

Secondary Review: K. Clark Swentzel K. Clark Swentzel 3/6/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbits [OPPTS 870-1200, OPP 81-2]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA64250 45WP-B (46.4% Propiconazole)

SYNONYMS: TILT 45WP

CITATION: J.O. Kuhn (18 April 1995) Acute Dermal Toxicity Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1856-95, 43655604, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: In this acute dermal toxicity study (MRID No. 43655604), a single dose (2020 mg/kg) of moistened test material was applied to the clipped, intact dorsal skin of male and female rabbits (5/sex) on Day 0. Application sites were covered with an occlusive dressing during the 24-hour exposure period. All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Body weights and body weight gains were, in general, unaffected by treatment. At terminal sacrifice (Day 14) no abnormalities were noted during the gross examination.

LD_{50} > 2020 mg/kg (males and females)

Toxicity Category III

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-2) for an acute dermal toxicity study in the rabbit.

MATERIALS and METHODS

Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Rabbit Strain: New Zealand White; Age: 3-6 months; Body Weight (kg): 2.600-2.925 (males), 2.375-2.875 (females); Source: Ray Nichols Rabbitry, Lumberton, TX; Food: Purina Rabbit Chow, *ad libitum*; Water: Tap water, *ad libitum;* Acclimation Period: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30-80%, Air changes: 10-12/hr, Light/dark cycle: 12hr/12 hr.

Study Design: On the day prior to treatment, the dorsal surface was clipped free of hair to expose an area not less than 10% of the total body surface area. Test material was moistened with distilled water and applied evenly to intact skin. The application site was covered with gauze, which was held in place with non-irritating adhesive tape and an occlusive dressing. After a 24-hour exposure, the occlusive dressing and gauze were removed and residual test material cleaned from the application site with tap water and a moistened cloth. During the day of dosing (Day 0) and once daily, thereafter, for 14 days, animals were observed for signs of toxicity, skin irritation (excluding Day 0), moribundity and mortality. Individual body weights were recorded just prior to dosing, and on Days 7 and 14 of the observation period. At the end of the observation period animals were necropsied for gross pathological examination.

Statistics: Not performed.

RESULTS and CONCLUSIONS

In this acute dermal toxicity study, a single dose (2020 mg/kg) of moistened test material was applied to the clipped, intact dorsal skin of male and female rabbits (5/sex) on Day 0. Application sites were covered with an occlusive dressing during the 24-hour exposure period. All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Body weights and body weight gains were, in general, unaffected by treatment. At terminal sacrifice (Day 14) no abnormalities were noted during the gross examination.

LD_{50} >2020 mg/kg (males and females)

Toxicity Category III

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-2) for an acute dermal toxicity study in the rabbit.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 27 Feb 96
Section II, Tox. Branch II (7509C)

Secondary Review: K. Clark Swentzel K. Clark Swentzel 2/28/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rats [OPPTS 870-1300, OPP 81-3]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA-64250 45WP-B (46.4% Propiconazole)

SYNONYMS: TILT 45WP

CITATION: J.O. Kuhn (20 April 1995) Acute Inhalation Toxicity Study in Rats, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1868-95, 43655605, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: Sprague-Dawley rats (5/sex/dose) were exposed to powder aerosols at concentrations of 1.69 and 5.54 mg/L for four hours and observed daily for 14 days. All animals survived to terminal sacrifice. Piloerection, decreased activity, ptosis and fur coated with feces and urine were observed in all animals for approximately four days post exposure. Animals were generally free of clinical signs by Day 4 or 5. Average MMAD values were 2.872 μm (1.69 mg/L) and 8.172 μm (5.54(mg/L). The total mass of particles having diameters of 1 μm and less was calculated to be 13.5% for both 1.69 mg/L and 5.54 mg/L, and diameters of 5 μm and less, 71.5% at 1.69 mg/L and 54% at 5.54 mg/L.

LC_{50} > 5.54 mg/L for males and females

Toxicity category IV

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-3) for an acute inhalation toxicity study in the rat.

MATERIALS and METHODS

Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Rat Strain: HSD: Sprague-Dawley SD; Age: 8-12 weeks; Body Weight (g): 210-247 (males), 213-243 (females); Source: Harlan Sprague-Dawley, Inc., Houston, TX; Food: Purina Formulab Chow # 5008, *ad libitum* (except during exposure period); Water: Tap water, *ad libitum* (except during exposure period); Acclimation Period: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30-80%, Air changes: 10-12/hr, Light/dark cycle: 12hr/12 hr.

Study Design: Rats (5/sex/dose) were exposed to powder aerosol of test compound at concentrations of 1.69 and 5.54 mg/L for four hours using a 500 L nose-only exposure chamber. Animals were observed for clinical signs of toxicity and mortality frequently during the day of exposure (Day 0) and daily, thereafter, for 14 days. Animals were weighed just prior to exposure and on Days 7 and 14. All animals were necropsied for gross pathological signs.

Test Atmosphere Generation and Test Chamber Conditions: Dust aerosols were generated from fine powdered test material. The 1.69 mg/L exposure level was generated by an Gem T Trost Air Mill which aspirated the test material from a motorized revolving disk system coupled to the mill, then elutriated the resulting aerosol through a baffling chamber. For the 5.54 mg/L exposure level, test material was aspirated (Venturi Aspirator) from a revolving disk delivery system. The concentrated aerosols were diluted with filtered air and drawn into the exposure.

Air flow, temperature, and relative humidity were recorded at 30-minute intervals during the exposure. Air flow was maintained 11.5 to 13.6 air changes per hour, which was sufficient to control the oxygen concentration to at least 19% during the exposure. Gravimetric analyses of the chamber atmosphere were performed at approximately 30-min intervals during the exposure. Particle size distributions were determined at 1¼ and 3¼ hours for the 1.69 mg/L test atmosphere and at 1 and 2¼ hours for the 5.54 mg/L test atmosphere.

Statistics: Body weight data were expressed as means and standard deviations.

RESULTS and CONCLUSIONS

Exposure Chamber Conditions: The mean (range) temperature and relative humidity within the exposure chamber were 73°F (72 - 73°F) and 89% (86-91%) at 1.6 mg/L, respectively, and 70°F (69-70°F) and 89% (86-90%) at 5.54 mg/L,

respectively; air flow was maintained at a constant 113 L/min during both exposures.

Test Atmosphere Analysis: Time-weighted concentrations (range) of test material were found to be 1.632 mg/L (1.366-1.894 mg/L) and 5.538 mg/L (4.978-5.903 mg/L); the T-99 for the low and high dose levels were 24 min and 20 min, respectively. Average MMAD values were 2.872 μm and 8.172 μm for the low and high test atmospheres, respectively. Although the average MMAD at 5.538 mg/L was greater than the 1 to 4 μm required for an acute inhalation study, the MMAD for the 1.69 mg/L (which is close to the limit dose) was within the recommended range. The total mass of particles having diameters of 1 μm and less was calculated to be 13.5% for both 1.69 mg/L and 5.54 mg/L and diameters of 5 μm and less, 71.5% (1.69 mg/L) and 54% (5.54 mg/L).

Clinical Observations and Mortality: All animals survived to terminal sacrifice. Clinical signs during the 14-day observation period included piloerection, decreased activity and ptosis were observed in all animals through Day 1 (5.54 mg/L) or Day 2 (1.69 mg/L); fur coated with feces and urine were observed in all animals through Day 1 (1.69 mg/L) or Day 4 (5.54 mg/L). Animals were generally free of clinical signs by Day 4 or 5.

Mean Body Weights: Compared to the Day 0 values, the mean body weights on Day 7 were slightly reduced in low-dose males (1.7%) and high-dose females(2.6 %). Mean body weights on Day 14 were increased in both dose groups.

Gross Pathology: Necropsy at terminal sacrifice did not reveal any abnormal gross pathological changes.

LC_{50} > 5.54 mg/L for males and females

Toxicity category IV

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§81-3) for an acute inhalation toxicity study in the rat.

Reviewed by: Robert F. Fricke, Ph.D. 011833
Section II, Tox. Branch II (7509C) Robert F. Fricke 2/29/96

Secondary Review: K. Clark Swentzel K. Clark Swentzel 2/29/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation- Rabbits [OPPTS 870-2500, OPP 81-5]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA-64250 45WP-B (46.4% Propiconizole)

SYNONYM: TILT 45WP

CITATION: J.O. Kuhn (17 April 1995) Primary Dermal Irritation Study in Rabbits, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1857-95, 43655607, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: In this study (MRID No.: 43655607), the dermal sensitization potential of test material was evaluated in NZW rabbits (3/sex). After a 4-hour exposure with 400 mg test material (moistened with deionized water), the application sites were cleaned of residual test compound and scored for edema and erythema (Draize method) within 30 min and at 24, 48 and 72 hr. After a 4-hour exposure the application sites were cleaned of residual test compound and scored. Very slight erythema (Draize Score = 1) was observed in 4/6 animals at 1/2 hr and 2/6 at 24 hr; no erythema or edema were observed at any other time points. Based on the PII value of 0.2, the test material was found to produce slight dermal irritation.

Toxicity category IV (PII = 0.2, slightly irritating)

This study is classified as **ACCEPTABLE** and satisfied guideline requirements (§81-5) for a dermal irritation study in the rabbit.

MATERIALS and METHODS

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Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Rabbit Strain: New Zealand White; Age: 3-6 months; Body Weight (kg): 2.625-2.900 (males), 2.650-3.000 (females); Source: Ray Nichols Rabbitry, Lumberton, TX; Food: Purina Rabbit Chow, *ad libitum*; Water: Tap water, *ad libitum;* Acclimation: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30-80%, Air changes: 10-12/hr, Light/dark cycle: 12hr/12 hr.

Study Design: The dermal irritation potential of the test material was evaluated in NZW rabbits (3/sex). The application sites (at least 8 cm x 8 cm) on the backs of the animals were clipped free of fur one day prior to dosing. On Day 0, 400 mg of test compound (moistened with 0.35 mL of deionized water) was applied to each test site and covered with surgical gauze (2.5 x 2.5 cm), which was secured with non-irritating adhesive tape and a non-occlusive dressing (orthopedic stockinette). The test compound remained in contact with the skin for 4 hours, at which time, the dressing and gauze were removed and application sites cleaned with water to remove any remaining residual test compound. After removal of the test compound, application sites were scored within 30 min and at 24, 48 and 72 hr for edema and erythema using the Draize method. Based on the scores, the Primary Irritation Index (PII) was calculated.

RESULTS and CONCLUSIONS

After a 4-hour exposure to 400 mg of test material (moistened with deionized water), the application sites were cleaned of residual test compound and scored for skin irritation. Very slight erythema (Draize Score = 1) was observed in 4/6 animals at 1/2 hr and 2/6 at 24 hr; all other time points were negative. No edema or erythema were observed at any other time points. Based on the PII value of 0.2, the test material was found to produce slight dermal irritation.

TABLE 2: INCIDENCE OF INDIVIDUAL ERYTHEMA AND EDEMA SCORES AND PRIMARY IRRITATION INDEX[a]

OBSERVATION	TIME AFTER UNWRAP			
	1/2 Hr	24 Hr	48 Hr	72 Hr
ERYTHEMA SCORE = 1	4/6	2/6	0/6	0/6
EDEMA SCORE = 1	0/6	0/6	0/6	0/6
PRIMARY IRRITATION INDEX	PII = 0.2			

[a] Data summarized from text table (pg 6) of the study.

Toxicity category IV (PII = 0.2, slightly irritating)

This study is classified as **ACCEPTABLE** and satisfied guideline requirements (§81-5) for an dermal irritation study in the rabbit.

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Reviewed by: Robert F. Fricke, Ph.D. Robert F Fricke 27 Feb 96
Section II, Tox. Branch II (7509C)

Secondary Review: K. Clark Swentzel K. Clark Swentzel 2/28/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pigs [OPPTS 870-2600, OPP 81-6]

EPA IDENTIFICATION NOs.:
PC Code: 122101
Caswell No.: 323EE
CAS No.: 60207-90-1
DP Barcode: D217197
Submission No.: S489753

TEST MATERIAL: CGA64250 45WP-B (46.4% Propiconizole)

SYNONYM: TILT 45WP

CITATION: J.O. Kuhn (20 April 1995) Dermal Sensitization Study in Guinea Pigs, Stillmeadow, Inc., Sugar Land, TX, Study No.: 1858-95, 43655608, unpublished

REGISTRANT: Ciba-Geigy Corporation, Ciba-Crop Protection, Greensboro, NC

EXECUTIVE SUMMARY: Buehler's method was used to evaluate the skin sensitization potential of the test material in guinea pigs. Following induction and challenge with 400 mg test material (moistened with 0.35 mL of deionized water), no dermal sensitization was noted in any of the treated animals. Naive control animals were also negative for dermal irritation, while DNCB-treated, positive control animals had a mean score of 1.8 after rechallenge.

Not a skin sensitizer

This study is **ACCEPTABLE** and satisfies guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

MATERIALS and METHODS

Test Compound: CGA-64250 45WP-B; Description: Tan powder; Batch No.: GP-940122; Other ID No.: FL-940165 Purity: 46.4% Propiconazole; Contaminants: Summarized in MRID No. 436556-02.

Test Animals: Species: Guinea pig Strain: Hartley Albino Age: 5-6 months Weight (g): 354-380 (males); 349-377 (females); Source: SASCO, Inc., Madison, WI; Food: Purina Certified Guinea Pig Chow, *ad libitum* Water: Tap water, *ad libitum*; Acclimation period: At least five days; Environmental: Temperature: 72 ± 5°F, Relative humidity: 30 - 80%, Air changes: 10-12/hr, Light/dark photocycle: 12 hr/12 hr.

Preliminary Dermal Irritation Study: A preliminary dermal irritation study was carried out on 2 males and 2 females to determine the maximum dose of test material producing no more than slight irritation, and the maximum nonirritating dose. Doses of concentrations of test material in deionized water. On the day prior to dosing, the backs of the four animals were clipped free of fur to expose an area at least 8 x 10 cm. On the day of dosing, 400 mg, moistened with 0.35 mL of deionized water, and 0.4 mL of 75%, 50% and 25% w/v were applied on the backs, covered with a gauze pad (1.6 x 2.8 cm) and secured with a piece of adhesive. The entire trunk of each animal was wrapped with clear polyethylene film. Following a 6-hour exposure, the wrappings and gauze were removed and the application sites cleaned of residual test material. Dermal irritation was evaluated 24 and 48 hr post-exposure.

Based on the results of the preliminary study, 400 mg of test material moistened with 0.35 mL of deionized water was found to be non-irritating.

Main Study

Induction Phase: Animals (5/sex/group) were randomly assigned to naive control and test groups. One day prior to dosing, the left side of the back was clipped free of fur. The treatment group received 400 mg of test material, moistened with 0.35 mL of deionized water, applied to the skin (left front quadrant of back) and covered with a 1.6 x 2.8 cm gauze secured to a piece of adhesive (Coverlet adhesive dressing). The entire trunk of each animal was wrapped in an occlusive dressing (plastic film). Animals were restrained during the 6-hour exposure period after which time the dressing and gauze were removed. This same procedure was repeated weekly, for three weeks. Application sites were scored for skin reaction approximately 24 hours after treatment.

Naive control animals remained untreated during the induction phase of the study.

Challenge Phase: Following a two-week resting period, application sites (right rear of the back) of naive control and test group animals were clipped free of fur and challenged with challenged with 400 mg test material moistened with 0.35 mL of deionized water as described above. After a 6-hour exposure, the application sites were scored for signs of irritation approximately 24 and 48 hr after removal of the dressing.

Positive Control Testing: In an independent positive control study, conducted from 11 January 1995 through 16 February 1995, 1-chloro-2,4-dinitrobenzene (DCNB) was used for the Induction Phase (1.0% w/v solution in 80% ethanol), Challenge Phase (0.1% w/v solution in acetone), and Rechallenge Phase (0.15% w/v solution in 80% ethanol). The positive control material produced a mean score of 1.8 after the rechallenge phase, compared to a naive control score of 0.6. This positive control study adequately validated the performance of the dermal sensitization study.

Scoring: A erythema scores (0 = no reaction; 0.5 = very faint, usually nonconfluent; 1 = faint, usually confluent; 2 = moderate; 3 = strong, with/without edema). The test material was considered to be a skin sensitizer if the mean irritation score for the test group was appreciably greater than the naive control group.

RESULTS and CONCLUSIONS

Test material was evaluated for dermal sensitization potential using Buehler's method. No dermal sensitization was noted in any of the treatment or naive control animals (mean challenge scores = 0.0).

Not a skin sensitizer

This study is **ACCEPTABLE** and satisfies guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.