13544

039585

Chemical:	**1H-1,2,4-Triazole, 1-((2-(2,4-dichloroph**
PC Code:	**122101**
HED File Code	**13000 Tox Reviews**
Memo Date:	***02/26/2002***
File ID:	**TX050446**
Accession Number:	**412-02-0281**

HED Records Reference Center
05/14/2002

Image 1

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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

TXR No. 0050446

MEMORANDUM

DATE: February 26, 2002

SUBJECT: Propiconazole: Review and Update of Toxicology Studies to Support Re-registration Eligibility Decision
P.C. Code: 122101 Case: 819508

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

TO: Eric Olson/Robert McNally (PM-60)
Reregistration Section
Special Review and Reregistration Division (7508C)

THRU: Sanjivani Diwan, Ph.D., Senior Toxicologist
and
Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TASK ID: DP Code: D269772, D272339, Submission: S587114, S591835

Registrant: Syngenta, USA

Action Requested: Update of Data Evaluation Records (DER's) for preparation of the Toxicology Chapter of the Re-registration Eligibility Decision Document

Agency's Action:

HED has prepared/or updated the executive summaries of the Data Evaluation Records (DER's)

on the subject studies in light of the new guidelines and classification systems. The updated executive summaries are attached.

Summaries of the following MRIDs is presented:
00058591, 00058592, 00058593, 00058594, 00058596, 00058597, 00058598, 00058600, 00058601, 00058602, 00058603, 00058606, 00058607, 00074506, 00074507, 00116591, 00129570, 00129918, 00130844, 00133343, 00133347, 00133348, 00133349, 00151502, 00151503, 00151505, 00151508, 00151509, 00151514, 00151515, 00151517, 00163164, 00164469, 00164795, 00164800, 40425001, 40425002, 40425004, 41326701, 42050501, 42050502, 42403901, 42415701, 45215801, 45345901, 93194026, 93194027, 93194029, 93194030, 93194031, 93194032, 93194033, 93194034, 93194035, 93194036, 93194037, 93194041, 93194044

A. SUBCHRONIC STUDIES

1. Subchronic Oral toxicity Study - Rat

In an acceptable/guideline subcronic toxicity study (MRID 00058606 & 93194032), CGA 64250 (Batch No. 35/1 P1, 90.0% purity) was administered to Tif (RAIF) SPF rats, approximately four weeks of age (20/sex/dose) at dietary concentrations of 0, 240, 1200, or 6000 ppm (0, 15.85, 76.08 and 461.73 mg/kg bw/day in males and 0, 16.82, 77.59 and 400.90 mg/kg bw/day in females, respectively) for 13 weeks.

No clinical symptoms nor any signs of local and/or systemic toxicity were observed. The survival and mean food consumption of animals was unaffected by the treatment. The body weight and body weight gain of all males and females at 6000 ppm was significantly decreased from weeks 2-13 (79% and 80% of controls body weight and 75% and 73% of controls body weight gain at week 13 for males and females, respectively). The body weight and body weight gain of the females from the 1200 ppm group was significantly decreased from weeks 9-13 when compared to the control (92% of controls body weight and 89% of the controls body weight gain at week 13). For all animals in the 6000 ppm groups, absolute organ weights (heart, kidney, and adrenal glands in males; kidneys and heart in females) were decreased and relative organ weights to body weight increased while organ to brain weight ratio mostly decreased.

Ophthalmic, auditory and hematological findings showed no evidence of treatment related effects. Erythrocyte count, hematocrit and hemoglobin concentration were found to be significantly lower in female rats of the high dose group at week 13. The only clinical chemistry findings noted consisted of an increase in alkaline phosphatase activity in the high-dose female rats at week 13 and an increase in the γ-glutamyl transpeptidase activity in male and female rats of the high-dose groups at weeks 4, 8, and 13. Histopathology examination of the spleen of all female rats from the 6000 ppm group showed an increase in hemosiderosis.

The **NOAEL** is considered 1200 ppm in males (76 mg/kg bw/day) and 240 ppm in females

(16.82 mg/kg bw/day). The **LOAEL** is 6000 ppm in males (462 mg/kg bw /day) and 1200 ppm in females (77.59 mg/kg bw/day) based on reduced body weight gain.

2. Subchronic Oral toxicity Study - Mouse

In an acceptable/guideline subcronic toxicity study (MRID 42050501), propiconazole was administered as CGA 64250 (92.0% purity, batch number FL-850083) to 7-week old Crl:CD-1 (ICR) BR (Swiss) mice (20/sex/dose) at dietary concentrations of 0, 20, 500, or 2500 ppm (0, 2.7, 65, 352 mg/kg/day in males and 0, 3.4, 85, 434 mg/kg/day in females, respectively) for 17 weeks. Two additional groups of **male** mice (20/group) were administered the test material at 850 or 1450 ppm (112, 194 mg/kg/day, respectively).

No clinical signs or mortality attributable to the treatment. Body weight and body weight gains and food consumption were not affected by treatment. Opthhthalmological examinations did not reveal any eye lesions.

Statistically significant increases ($p < 0.01$) in liver weights (absolute: 115%-192% of control, and relative to body weight: 113%-204% or relative to brain weight: 116%-194%) were found in the male animals at ≥500 ppm and in the female mice at the 2500 ppm (179% of control, 184% relative to body weight and 189% relative to brain weight).

Gross pathological examination of the livers from the male mice revealed a significant increase in liver enlargement (≥1450 ppm) and focal discoloration (≥850 ppm). The female mice showed a significant increase in liver enlargement at 2500 ppm; focal discoloration was present at 2500 ppm. The increase in absolute and relative liver weights also correlated well with histopathological (hypertrophy and necrosis) and clinical chemistry (increases in both ALT and AST) findings. Males showed significant decreases ($p<0.01$) in serum cholesterol at ≥ 1450 ppm after 13 weeks and at ≥850 ppm. Significant increase ($p<0.01$)in alanine aminotransferase occurred after 17 weeks in males at ≥ 1450 ppm and in females at 13 and 17 weeks at 2500 ppm. Aspartate aminotransferase increased significantly ($p<0.01$) in females at the 17 week interval at 2500 ppm. Clinical chemistry analysis was limited to liver only. Hematology was not performed.

Male mice showed a dose-related increase in both the incidence and severity of histopathological lesions of the liver, while the females showed significant increases only at 2500 ppm. At 500 and 850 ppm dose levels, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 for animals in the 1450 and 2500 ppm groups, respectively. In females at the 2500 ppm dose, 14/20 showed minimal to mild hypertrophy, while 3/20 were classified as moderate. Necrosis occurred both as scattered individual cell foci and multicellular areas. Necrosis was present in males at 500 ppm with significant increases found at ≥850 ppm. The severity and incidence of the necrosis for males in the 1450 ppm group was minimal for 2/20, mild for 5/20 and moderate for 1/20. At 2500 ppm 7/20 and 5/20 male mice showed minimal and mild necrosis, respectively. For females at 2500 ppm 6/20 showed

mild necrosis. Cellular necrosis in males was minimal for 2/20 at 1450 ppm and 7/20 at 2500 ppm and mild for 5/20 at 2500 ppm.

Vacuolation also occurred as scattered individual foci and multicellular areas. Significant vacuolation was present only in the 2500 ppm group where 2/20, 7/20 and 1/20 showed minimal, mild and moderate vacuolation, respectively. No compound-related effect was found when sections of male livers were stained using Oil Red 0, since nearly all of the sections (including the controls) were stained for microvesicular lipid.

Males appeared to be more sensitive to the test article than females. The **LOAEL** based on increase in absolute and relative liver weights and histopathological changes (hypertrophy, necrosis) is 500 ppm (65 mg/kg/day) in males and 2500 ppm (434 mg/kg/day) in females. The **NOAEL** is 20 ppm in males (2.7 mg/kg/day) and 500 ppm in females (85 mg/kg/day).

3. Subchronic Oral toxicity Study - Mouse

In an acceptable subcronic toxicity study (MRID 42050502) propiconazole administered as CGA 64250 (92.0% purity, batch number FL-850083) was administered to 37 days old Crl:CD-1 (ICR) BR Swiss **male** mice (40/dose) at dietary concentrations of 0, 20, 500, 850, 1450 or 2500 ppm (0, 2.7, 65, 112, 194, 352 mg/kg/day, respectively) for 13 weeks. One group of 10 males/dose was sacrificed after 4 weeks, a second group of 10 males/dose after 8 weeks and the third group of 20 males/dose was sacrificed after 13 weeks. This study was conducted to determine the maximum tolerated dose (MTD).

No clinical signs and mortality attributable to the administration of the test article were reported. There were no treatment-related eye lesions noted.

Significant differences in weekly body weights between the control and treated mean body weights were limited to animals in the 2500 ppm group during the first 8 weeks of the study. A significant difference was also observed for the 1450 ppm group after 4 weeks. The mean cumulative body weight gains showed significant decreases ($p < 0.01$) for animals in the 2500 ppm during weeks 1, 2, and 4(36%, 70%, 70% of the body weight gain of the controls, respectively); by week 8 the decrease in body weight gain was 11%. Although the food consumption at 2500 ppm was comparable to controls, the males at 2500 ppm had lower food efficiency (-0.7% vs 1.4% in controls).

Statistically significant (< 0.01) increases in liver weights (absolute:116%-182% of controls, and relative to body weight: 118-194% of controls, and relative to brain weight: 119-192% of control) were found in the male animals at ≥500 ppm at the end of the treatment period. Gross pathology examinations revealed generalized enlargement and focal discoloration of the livers at ≥850 ppm.

Hepatocellular hypertrophy, necrosis and vacuolation of the liver significantly increased at ≥500

ppm at all sacrifice times. In general, the severity of the histopathological lesions was dose related with the highest incidence of mild to moderate lesions occurring in the highest dose groups. None of the lesions were classified as either marked or severe.

Serum cholesterol significantly decreased ($p<0.01$) at ≥850 ppm and serum alanine aminotransferase (a serum enzyme associated with hepatic necrosis) and sorbitol dehydrogenate increased at ≥1450 ppm and ≥850 ppm, respectively. Only liver enzymes were measured.

The **LOAEL** is 500 ppm (65 mg/kg/day), based on increase in absolute and relative liver weights and histopathological liver lesions (hypertrophy, necrosis, vacuolation) seen at 4, 8 and 13 weeks of sacrifice. The **NOAEL** is 20 ppm (2.7 mg/kg/day).

4. Subchronic Oral toxicity Study - Mouse

In this acceptable/non-guideline study (MRID 45215801) all liver sections from the subchronic study in CD-1 mice (MRID 42050502) were reexamined by a second pathologist to compare the liver lesions with those from a subsequently conducted 18-month oncogenicity in CD-1 mice (MRID 44381401) by resolving differences in terminology and the diagnostic criteria used to score the severity of symptoms.

Reexamination of the liver sections from the subchronic study confirmed the histologic evidence of hepatotoxicity at all dose levels and at all sacrifice intervals (4, 8 and 13 weeks) consisting of hepatocellular hypertrophy, monocelluar necrosis (individual hepatocytes), necrosis (small groups of hepatocytes)and fatty change (vacuolation of the liver). Hepatocelluar hypertrophy was seen in both studies at ≥500 ppm at 9 and 8-week sacrifice. The monocellular necrosis, necrosis and fatty changes, were seen ≥1450 ppm in the subchronic study at 9 week sacrifice while the same findings in the 18-month study were seen at 850 ppm (the highest dose tested) at the comparable 8 week sacrifice.

It was concluded by the study author that male mice in the 18-month oncogenicity study were more sensitive to the hepatotoxic effects of CGA-64250 because effects seen at 850 ppm, the dose that caused tumor induction in the 18 month study, showed presence of fatty change, moncellular necrosis and necrosis (at 9 weeks) which were not seen in the 13-week study at the same point (at 8 weeks). This finding does not change the overall NOAEL and LOAEL of 20 and 500 ppm, respectively (2.7 and 65 mg/kg/day, respectively) observed in the original study.

5. Subchronic Dermal Toxicity - Rabbits

In an acceptable/guideline repeated dose dermal toxicity study (MRID 00116591 and 93194034), groups of 20 New Zealand rabbits received 15 daily dermal applications of 0 (11 males and 9 females), 3 (11 males and 9 females), 30 (10 males and 10 females), or 300 (13 males and 7 females) mg/kg/day propiconazole technical(90.7%, Batch No. FL-810858) over a 21-day period. The test material was applied on the intact and abraded skin with an impervious cuff for

6 hours for five days a week for three weeks.

There were no treatment-related deaths or signs of systemic toxicity and no treatment-related effects on body weight, food consumption, or opthalmology, hematological and clinical chemistry parameters. There were no compound related gross necropsy, organ weight effects or histopathological findings.

Skin irritations were noted in the 30 and 1000 mg/kg/day groups beginning at day 2 and persisted for the remainder of the study with maximum irritation indexes of 1.0 and 4.1, respectively. Signs of irritation were noted in the 3.0 mg/kg/day group beginning on day 15 in males only with the highest irritation index of 0.3 at day 19.

There were mild to moderate skin lesions which were dose related in treated animals compared to controls. Hyperkeratosis, acanthosis, mild dilation of blood vessels and mononuclear cells and/or heterophils in the proximal dermis were noted in a dose related manner.

The **LOAEL** for systemic effects was >1000 mg/kg/day (the highest dose tested). The **NOAEL** for systemic effects is 1000 mg/kg/day. The **LOAEL** for skin effects was 3 mg/kg/day based on mild dermal irritation (Hyperkeratosis, acanthosis, mild dilation of blood vessels and mononuclear cells and/or heterophils in the proximal dermis) at 3 and 30 mg/kg/day and moderate dermal irritation at 1000 mg/kg/day. No **NOAEL** for skin lesions was established.

6. Subchronic Toxicity Study - Dogs

In an acceptable/guideline sub-chronic toxicity study (MRID 00058607, 93194033), CGA 64250 technical(88.0% purity, batch number 35/5) was administered to pure-bred Beagle dogs (4/sex/dose; 19-28 weks old; 7.9-13.0 kg for males and 6.0-11.6 kg for females) at dietary concentrations of 0, 50, 250, or 1250 ppm (0, 1.25, 6.25, 31.25 mg/kg/day based on a dose conversion factor for dogs of 1 ppm = 0.025) for 13 weeks. The dogs were housed in kennels equipped with underfloor heating.

Some animals of all groups including controls showed slight to moderate diarrhea during the whole study. Survival, body weight gain, food consumption, clinical chemistry, urinalysis, ophthalmic and auditory examinations and organ weights revealed no treatment related effects.

Necropsy showed that in 3/4 of male dogs from the highest dosage group (1250 ppm), slightly granular surface in the pyloric and propyloric part of the stomach was noted. Apart from this finding no gross anatomical changes were seen neither in treated nor in control dogs. Microscopically, in 3 out of 4 male dogs from the highest dose-group and 1 out of 4 female dogs from the 250 ppm group slightly increased amount of lymphoid follicles in the mucous membrane of the pyloric part of the stomach was seen. However, this was not seen in the high dose females. These histological findings are considered compound-related.

The **LOAEL** is 250 ppm (6.25 mg/kg/day) based on the finding of lymphoid follicles in the mucous membrane of the pyloric part of the stomach. The **NOAEL** is 50 ppm (1.25 mg/kg/day).

B. CHRONIC STUDIES

7. Chronic Oral Toxicity (Dietary) Study - Dogs

In an acceptable/guideline chronic toxicity study (MRID 00151515), propiconazole was fed as CGA-64250 technical (90.2% purity, batch # FL-831527) to beagle dogs (7/sex/dose (control and high dose) and 5/sex/group (low and mid dose groups) at dietary dose levels of 0, 5, 50 or 250 ppm (time weighted average dietary concentrations based on mean food consumption are: 1.2±0.2, 13.0±2.0, 59.0±8.0 mg/kg/week or 0.2, 1.9, 8.4 mg/kg/day for males and 1.3±0.2, 13.0±2.0, 62.0±10.0 mg/kg/week or 0.2, 1.9 , 8.9 mg/kg/day for females, respectively) for a period of 52 weeks. These doses were based on a 3-month study in dogs fed 50, 250 or 1,250 ppm where a LOAEL of 250 ppm was set based on changes in the pyloric region of the stomach. All animals were sacrificed after 52 weeks except for two males and two females of the control and 250 ppm were sacrificed after a four week recovery period during of which these dogs were fed diets free of CGA-64250.

All dogs survived the 12 month treatment. No treatment related effects were noted in mean body weights, body weight gains, mean food consumption, hematologic and clinical chemistry, opthalmological findings, electrocardiograms, organ weights and gross pathological findings.

Histopathologic examinations revealed hypermia of the mucosa of the stomach in 3/5 of the 250 ppm males, and no comparable findings were seen in the control males. **Functional hypertrophy of the mammary gland** was reported in 1/5 control females, 2/5 receiving 50 ppm, and 3/5 receiving 250 ppm of the test material. All other findings including the necropsy and histopathological examination of the dogs in the recovery period were unremarkable.

The **LOAEL** is 250 ppm (8.4 mg/kg/day), based on hypermia of the stomach in males (indicating mild irritation of the mucosa). The **NOAEL** is 50 ppm (1.9 mg/kg/day). However an OHEA and OPP work group (May 25, 1987) recommended instead the usual dose conversion factor for dogs of 1 ppm = 0.025 for estimation of the NOAEL. This revision results in slightly lower **NOAEL** of 1.25 mg/kg/day. Accordingly the **LOAEL** is revised to 6.25 mg/kg/day

8. Chronic Oncogenicity Study - Mouse

In an acceptable/guideline 24-month oncogenicity study (MRIDs 00129570, 00151503, 00130844 and 93194037), CGA 64250 technical (Batch No. P4-6, 87.2-91.9% purity) was administered to groups of CD-1 mice (52/sex/dose) in the diet at concentrations of 0, 100, 500, or 2500 ppm (10.0, 49.4, and 344.3 mg/kg/day for males and 10.8, 55.6 and 340.3 mg/kg/day for females, respectively). A satellite group (12 mice/sex/dose) was sacrificed at one year. Diets were prepared weekly.

An increase in mortality was noted in males of the 2500 ppm group during the first 6 months. This finding is considered compound-related. Survival at 104 weeks for the control, 100, 500 and 2500 ppm groups was 46%, 38%, 40%, and 27% for the males and 54%, 63%, 46% and 62% for the females, respectively. .

Sporadic decreases in body weight gain, particularly in the high dose male and female groups were noted. Food consumption was increased in high dose male mice only.

There were no compound-related effects on hematological parameters examined. SGPT and SGOT were significantly increased in high dose males and females at 52 weeks and in high dose males at 100 weeks. SAP was increased in high dose males at week 100. These changes are considered indicative of liver damage. Urinalysis results did not reveal any treatment-related effects.

Increased liver weight was noted in high and mid dose males and in high dose females both at interim and terminal sacrifice. There was good correlation between gross and microscopic findings. Enlarged livers containing gross pathological changes were seen in high dose animals. Non-neoplastic changes in high dose males and females consisted of hepatocyte enlargement, vacuolation and fat deposition. Liver histopathology of low and mid dose mice was comparable to those of controls.

Necropsy observations at the termination of the study indicated a treatment-related increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly) among mid- and high-dose males (150% and 140% of controls, respectively) and in high-dose females (367% of control).

CGA 64250 treatment was associated with early expression of malignant liver cell tumors in male mice. The incidences of malignant (presumably carcinomas) liver tumors at the one year interim sacrifice were 0/11, 0/11 1/11, and 3/9 in the control, low, mid and high dose males, respectively. No liver tumors were found in any of the female mice sacrificed at the 1-year interim sacrifice.

The total incidences of combined liver adenomas/carcinomas in males for the control, 100, 500 and 2500 ppm groups were 28/64, 14/64, 25/62 and 48/64, respectively. For females the incidence was 5/64, 1/64, 2/64 and 8/64 in the control, 100, 500 and 2500 ppm groups, respectively. The combined incidence of liver tumors was statistically significant ($p < 0.001$) at the high dose level for males.

Male mice given CGA 64250 technical at 2500 ppm in the diet developed liver tumors. The **LOAEL** was 500 ppm (49.5 mg/kg/day) based on non-neoplastic liver effects (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly). The **NOAEL** was 100 ppm (10 mg/kg/day).

9. Chronic Oral Toxicity Study - Rats

In an acceptable/guideline 24-month oncogenicity study (MRIDs 00129918 and 93194035), CGA 64250 technical (Batch No. P4-6; 87.2-91.9% purity) was administered to groups of Sprague Dawley CD rats (50/sex/dose) in the diet at concentrations of 0, 100, 500, or 2500 ppm (3.6, 18.1 and 96.4 mg/kg/day for males and 4.6, 23.3 and 100.6 mg/kg/day for females, respectively). A satellite group (30 rats/sex) was included at each concentration level. Of these, 10 rats/sex were used for hematological investigation, another 10/sex for blood chemistry and urinalysis investigations and the other 10/sex for interim sacrifice at one year and detailed microscopic examination with organ weight analysis.

There were no compound-related clinical signs. Survival was not affected by the treatment. Food consumption was significantly lower ($p < 0.001$) for high dose females throughout the study and for high dose males from week 27 to termination ($p < 0.01$). Body weight gains of high dose male rats were significantly lower ($p < 0.001$; 84% of control during the first year, and 83% of control over the two year period). High dose female rats showed reduced body weight gain ($p < 0.001$; 65% of control during the first year and 66% of control during the entire two years, $p < 0.05$). These decreases in body weight gain were compound-related.

No toxicologically significant treatment-related effects were noted in hematology, blood chemistry and urinalysis parameters or in the ophthalmoscopy or hearing tests.

No macroscopic findings in rats sacrificed at 52 weeks were considered to be related to treatment. Liver weights were increased in high dose animals ($p < 0.001$; 122% and 144% of controls for males and females, respectively) at 52 weeks. Lipid deposition in liver cells was also increased in high dose males (6/10 vs 2/10 in controls). Liver weights were also increased in high dose animals ($p < 0.001$; 125% and 121% of controls for males and females, respectively) at termination. Necropsy observations showed an increased incidence of grossly enlarged livers among high dose males which died during the study or were sacrificed at termination (18/45 vs 6/40 in controls for males and 19/45 vs 12/28 in controls for females at termination). Also, an increased incidence of discolored foci or puncta were found in the lungs of high dose females (17/45 vs 4/28 in controls at termination).

An increased incidence of foci of enlarged liver cells in high dose females was reported (13/67 vs 1/67 in controls) and it was concluded that to be a treatment related effect (MRID 07391829; HED doc. No. 005352).

Livers of high dose males showed increased vacuolated hepatocytes (44/65 vs 26/64 in controls) and ballooned cells (25/65 vs 15/64 in controls) which also exceeded historical control range suggesting a treatment-related effect (MRID 07391829; HED doc. No. 005352).

A dose-related increase in liver cell lipid deposition in males was also apparent (4/64, 7/67, 15/66 and 17/65 in control, low, mid and high dose groups, respectively).

Additionally, the pancreas showed a dose-related effect in exocrine atrophy in female rats (1/60, 3/61, 6/62 and 9/65 in control, low, mid and high dose groups, respectively). The toxicological significance of this finding is considered questionable, however, since the incidence in the 2500 ppm group was comparable to the overall historical control value (MRID 07391829; HED doc. No. 005352).

Luminal dilatation of the uterus also appeared to be a dose-related effect (4/58, 10/63, 9/63, 17/65 in control, low, mid and high dose groups, respectively). The incidence of this finding in the 2500 ppm group exceeded both the concurrent and overall historical control values (MRID 07391829; HED doc. No. 005352) and was considered treatment-related.

There were no treatment-related increase in the incidence of malignant tumors in treated rats.

The incidence of dermal fibroma was increased in the high dose males (5/61 vs 0/59 in the control). There was also an apparent increase in thyroid follicular adenocarcinoma (3/67) in high dose females vs 0/59 in controls. Additional data subsequently submitted by the registrant (Accession No. 07391829) in regard to these lesions revealed that because there was no dose-related trend in the incidences of dermal fibromas (8%) in males and thyroid follicular cell adenocarcinomas in females (2/67; 3%) at 2500 ppm and the incidences were within their respective historical range, the occurrence of these was not considered to be treatment-related.

The **LOAEL** for CGA-64250 is 2500 ppm (96.4 mg/kg/day) based on liver lesions (vacuolation of hepatocytes in males, ballooned cells in the liver of males, foci of enlarged hepatocytes in females, and increased incidence of luminal dilation of the uterus) and reduced body weight gain in both males and females. The **NOAEL** is 500 ppm (18.1 mg/kg/day). The test material was not carcinogenic at the doses tested.

C. DEVELOPMENTAL STUDIES

10. Prenatal Developmental Study - Rat

In an acceptable/guideline developmental toxicity study (MRID 40425001), CGA 64250 technical(92.1% purity, Batch no. FL 850083) was administered to 24 CL:COBS CD (SD) BR VAF/PLUS virgin female rats/dose by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 30, 90 or 300 mg/kg/day from days 6 through 16 of gestation. High dose animals initially received 360 mg/kg/day up to five days, but because of severe symptoms it was reduced to 300 mg/kg/day.

Severe compound-related maternal toxicity (lethargy, ataxia, salivation, and biologically significant increases in rales, prostration, hypothermia and bradypnea) was observed at the high dose level during the first five days of dosing beginning on day 8 of gestation at 360 mg/kg/day. After lowering the dose to 300 mg/kg/day on day 6, the severity and frequency of these effects decreased rapidly. At the lower doses with the exception of one animal of the 90 mg/kg/day

group exhibiting rales, there were no treatment related clinical observations. In another separate study (MRID 40425002) imazalil was administered to a large number of pregnant females during gestation day 6-17 at 0 (178 females) or 300 mg/kg/day (179 females). In this study severe clinical toxicity (ataxia, coma, lethargy, prostation, labored respiration and salivation) was reported in treated animals.

Mean food consumption was significantly reduced ($p<0.05$) in the 300 mg/kg/day group on days 7-8, 8-9 and 9-10 and in the 90 mg/kg/day group on days 8-9 and 10-11. Maternal body weights were not affected by the treatments. Maternal body weight gains were significantly decreased ($p<0.05$) in the 90 mg/kg/day group (44% of controls) and in the high dose group (38% of controls) during gestation days 6-8 only. No significant treatment-related effects on uterine weights, corpora lutea, live and dead fetuses, fetal weights, and resorption were reported.

Based on the combined findings of this study and study MRID 49425002, the maternal toxicity **LOAEL** of Propiconazole is 300 mg/kg/day, based on severe clinical toxicity (ataxia, coma, lethargy, prostation, labored respiration and salivation). The maternal toxicity **NOAEL** is 90 mg/kg/day.

Fetotoxic effects observed included a high incidence of rudimentary ribs, though not statistically significant but part of dose related trend (0.7%, 3% and 39% in the 30, 90 and 300 mg/kg/day groups, respectively vs 0% in the controls), a high incidence of unossified sternebrae (57%, $p \leq 0.05$ in the 90 mg group, and 72%, $p \leq 0.01$ in the 300 mg group vs 38% in the controls), as well as increased incidence of shortened renal papillae(26% in the 90 mg group (not statistically significant) and 39% in the 300 mg group, $p \leq 0.01$ vs 23% in the controls) and absent renal papillae (5% in the 90 mg group (not statistically significant) and 11% in the 300 mg group, $p \leq 0.01$ vs 3% in the controls) and dilated ureter (43% in the 300 mg group, $p \leq 0.01$ vs 27% in the controls). External and visceral examination revealed a very low incidence of cleft plate malformations in the 90 mg group (0.3%) and in the 300 mg group (0.7%). The cleft palate finding at 300 mg/kg/day was also confirmed in the MRID 40425002 study.

The developmental toxicity **LOAEL** of Propiconazole is 90 mg/kg/day, based on increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae. The developmental toxicity **NOAEL** is 30 mg/kg/day.

11. Prenatal Developmental Study - Rat

In a non guideline/acceptable developmental toxicity study (MRID 40425002), CGA 64250 technical(92.1% purity, Batch No. FL 850083) was administered to CL:COBS CD (SD) BR VAF/PLUS virgin female rats by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0 (179 females) or 300 mg/kg/day (189 females) from days 6 through 15 of gestation.

Severe maternal toxicity (ataxia, coma, lethargy , prostration, audible respiration, labored respiration, and salivation, ptosis, lacrimation, pale color and death) was observed in the treated animals during the treatment period beginning on gestation day 6.

Mean food consumption was significantly lower (60-92% of the control values, $p<0.05$) in the treated group during the dosing period. Body weight gains were significantly lower (68% of controls, $p<0.05$) in dosed animals during GD 6-16.

There were no significant differences between dosed and control animals with respect to fetal sex ratio or mean number of corpora lutea, implantation sites and dead fetuses. The mean number of live fetuses was significantly (95% of controls, $p<0.05$) lower in dosed animals, due to lower mean implantation sites, and higher mean total resorption in the dosed animals, although not significantly different from controls. Mean fetal weights for both males and females (95% of controls, $p<0.001$) were significantly lower in dosed animals.

Fetuses were examined for external abnormalities only and there were no statistically treatment related , external, gross observations among fetuses. Cleft palate was reported in 2/2064 fetuses of dosed animals and 0/2122 of control fetuses. The incidence of cleft palate in controls for all teratology studies (not including this one) conducted at this laboratory during 1983-1985 was 0/5431. This study confirms the findings of cleft palate in the previous guideline study (MRID 40425001).

12. Prenatal Developmental Study - Rabbit

In an acceptable/guideline developmental toxicity study (MRID 00164800, MRID 40425004), CGA 64250 technical(Batch No. FL850083, 92.1% purity) was administered to groups (19/group) of artificially inseminated New Zealand white rabbits by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 100, 250 or 400 mg/kg/day from days 7 through 19 of gestation.

One animal from each of the mid-dose groups was found dead. In high-dose animals, 5/19 does were sacrificed early due to abortion or early delivery (statistically significant, $p<0.05$ compared to control 1/19). In the mid dose(250 mg/kg/day) group, one doe aborted early. One control animal delivered early.

Among animals of the high dose group, an increased incidence of stool alterations (decreased/no/soft; 18/19 vs 11/19 in controls, $p<0.05$) was observed, possibly compound related.

During the dosing period (days 7-19), the high and mid dose animals had a significant ($p<0.05$) decrease in food intake (43 - 63% of the controls and 58-78% of the controls in the high- and mid-dose groups, respectively) and a severe decrease in the maternal body weight gain, but rebounded to normal after withdrawal of the test compound. During GD 7-10, the maternal

animals had a weight loss of 0.047 and 0.111 kg at 250 and 400 mg/kg, respectively, compared to a weight gain of 0.018 kg in controls. The weight gains during GD 10-20 were 67-77% and 11-43% of controls at 250 and 400 mg/kg/day, respectively. An increased incidence of the formation of 13th rib was observed at 400 mg/kg/day. The incidence of this finding on fetuses/litter basis was 2.7, 3.9, 4.1 and 5.3 at 0, 100, 250 and 400 mg/kg/day, respectively. The incidence of fetuses at 40 mg/kg/day with this finding was statistically significant. Therefore, this finding was considered to be treatment-related. The increase in the number of resorptions at 400 mg/kg/day was caused by the resorption of an entire litter. At 400 mg/kg/day there was also an increased incidence of abortions.

The maternal toxicity **LOAEL** of Propiconazole in the rabbit is 250 mg/kg/day, based on reduced maternal body weight gains and decreased food consumption during the dosing period. The maternal toxicity **NOAEL** is 100 mg/kg/day.

The developmental toxicity **LOAEL** was 400 mg/kg/day based on increased incidence of fetuses/litters with 13th rib and increased abortions. The developmental toxicity **NOAEL** was 250 mg/kg/day.

13. Reproduction Study - Rat

In aan acceptable/guideline 2-generation reproduction study (MRIDs 00151514, 00163164, and 93194041), CGA 64250 technical(89.7% purity, FL-830377) was administered to groups of 15 male and 30 female Charles river CD rats at dose levels of 0, 100, 500 or 2500 ppm/group (mean doses of 8, 42 and 192 mg/kg/day for F0 males, 9.4, 43, 223 mg/kg/day for F0 females, 9.2, 48, 238 mg/kg/day for F1 males and 10, 52, 263 mg/kg/day for F1 females) in the diet. Test diets were administered to both F0 and F1 generation rats during pre-mating period and throughout gestation and lactation periods.

No compound-related clinical observations or mortality were reported. Female body weights in the F_0 and F_1 generation were significantly reduced in the high dose group at most of the body weight intervals(82-94% of the controls, $p<0.05$ and 0.01); body weight gains were also significantly reduced during pre-mating (12 weeks)as well as gestation and lactation periods(77-85% of controls, $p<0.01$). Correspondingly, high dose females also had significantly reduced food intake (83-88% of controls). In the F_0 and F_1 generation male body weights were reduced in the high dose groups compared to controls (not statistically significant); body weight gains in this group was 91-94% of controls for the premating period and during the entire duration of the study (7 months). Food consumption was reduced significantly in high dose F_0 males at week 1 (65% of the control, $p<0.01$) and week 7 (86% of the control, $p<0.01$) and in high dose F_1 males and females at week 2, 6 and 10 (84-88% of controls).

Hepatic "cellular swelling" was significantly increased in mid- dose males and high-dose males and females of the F_0 generation. In the F_1 parental animals, increase in the incidence of this finding was significant for both sexes in the mid- and high-dose groups. The incidence of

"hepatic clear-cell change" was significantly increased in F_0 high-dose males, F_1 mid-dose and high-dose males and F_1 high-dose females ($p<0.05$). The **LOAEL** for parental toxicity based on increased incidence of "hepatic clear cell change" is 500 ppm (42 mg/kg/day) and the **NOAEL** is 100 ppm (8 mg/kg/day).

Reproductive parameters were comparable in all groups. The number and percent of viable pups at birth and surviving through weaning were comparable between the dose groups and controls for both the F_{1a} and F_{1b} litters. In the F_{2a} litters, however, the number of pups delivered, delivered viable and surviving to day 4 of lactation were significantly ($p<0.01$) reduced in the high-dose group. The percentages of high-dose pups delivered viable and surviving to day 4 were also reduced (not statistically significant). The F_{2b} litters of these dams had significantly reduced survival rates (both number and percent of surviving pups) at lactation days 7, 14, and 21.

The mean body weights of high-dose progeny were significantly reduced at days 14 and 21 for pups of both generations (72-81% of controls). Reductions were also significant on days 4 and 7 (except for F_{1b} litters) and at birth (F_{2b} litters only). At necropsy, no treatment related anomalies, organ weight changes and gross pathology findings were noted in pups.

Histopathological evaluation of selected organs from F_{1b} and F_{2b} progeny revealed significantly ($p<0.01$) increased incidences of hepatic "cellular swelling" in high-dose males and females Attachment 2). This was considered to be a compound related effect.

The **LOAEL** and **NOAEL** for developmental toxicity are at 2500 ppm (192-263 mg/kg/day) and 500 ppm (43-52 mg/kg/day), respectively, based on decreased offspring survival and body weights and an increased incidence of hepatic lesions (cellular swelling) at 2500 ppm.

D. MUTAGENICITY STUDIES

14. Bacterial Reverse Mutation Assay

In a plate incorporation assay (MRID No. 00058601), *Salmonella typhimurim* strains were exposed to CGA 64250 (Batch No. Jn 18/5 F 1-2; purity not specified) at 25, 75, 115, 675 or 2025 µg/plate, both in the presence and absence of a rat microsomal activation system. Positive controls were tested.

No mutagenic effect was noted with or without microsomal activation at the various concentrations of CGA 64250. The study is classified **Unacceptable/guideline** (the test material purity was not specified nor the test material was tested at high enough concentration of 5000 µg/plate or up to a cytotoxic dose).

15. Mitotic Gene Conversion Assay

In an acceptable/guideline mitotic gene conversion assay in *Saccharomyces cerevisiae* (MRID

00133343) CGA 64250 technical (Batch No. Op. 103119; purity 90.7%) was tested at 0 (DMSO control), 10, 30, 90, or 270 µg/ml concentrations (with and without microsomal activation). Positive control was 4-nitroquinoline-N-oxide at 0.2 µg/ml(without microsomal activation) and cyclophosphamide at 300 µg/ml(with microsomal activation).

Under the experimental conditions of the this study, CGA 64250 technical did not induce mutation in *Saccharomyces cerevisiae* cells with or without metabolic activation.

16. Micronucleus Test - Chinese Hamsters

In an acceptable/guideline micronucleus anomaly test (MRID No. 00058603), propiconazole as CGA 64250 (Batch INA 35/1 P1, purity 90.0%) was administered by gavage at dosages of 251, 502 or 1004 mg/kg in 20 ml/kg PEG 400 to groups of 6 male and 6 female Chinese hamsters each. Treatment consisted of one daily application on 2 consecutive days. The animals were sacrificed 24 hours after the second application. Smears were made from the bone marrow.

One male animal from the highest dose group died after the second application. Bone marrow smears from CGA 64250 treated animals showed no significant difference from the control. By contrast, a positive control experiment with cyclophosphamide (128 mg/kg) yielded 8.92% cells with anomalies of nuclei. This is significantly different from the controls treated with the vehicle (PEG 400) alone.

17. Dominant Lethal Assay - Mouse

In an acceptable/guideline dominant lethal study (MRID No 00058602), propiconazole as CGA 64250 (Batch INA 35/1 P1, purity 90.0%) was administered by oral gavage as single doses of 165 or 495 mg/kg to groups of 20 male albino mice Tif:MAG F (SPF) which were then each mated to two untreated females from the same strain over a period of 6 weeks. At the end of each week the females were replaced by new ones.

Females mated to CGA 64250 treated males did not differ significantly from the females mated to controls, in mating ratio, the number of implantations and embryonic deaths (resorption). Pregnancy rates of females mated to the treated males were comparable to the females mated to controls. It was concluded that no evidence of dominant lethal effects was observed in the progeny of male mice treated with CGA 64250.

18. Unscheduled DNA Synthesis - Mammalian Cells: Human Fibroblasts

In an acceptable/guideline unscheduled DNA assay (MRID 00133347, MRID No. 0000151508) CGA 64250 technical (Batch No. Op. 103119, 90.7% a.i.) was tested for DNA-damaging properties on human fibroblasts *in vitro* at concentrations of 0, 0.07 µg/ml, 0.37 µg/ml, 1.86 µg/ml and 9.32 µg/ml (highest concentration selected was calculated to allow at least 25% cell viability). Two negative controls were used: one containing the vehicle and one untreated.

Positive control was 4-nitroquinoline-N-oxide (5 μM). ^{3}H-thymidine was added to treated and control cultures of human fibroblasts. Autoradiographs were prepared and 4 slides (50 cells/slide) were scored (silver grains counted) for each treated and control group. Mean values were reported in the original report of the study. No evidence of CGA 64250 technical induced DNA damage was found at concentrations up to and including 9.32 μg/ml.

19. Unscheduled DNA Synthesis - Mammalian Cells: Rat Hepatocytes

In an acceptable/guideline unscheduled DNA assay (MRID 00133348, 00151509, 93194044) CGA 64250 technical (Batch No. Op. 1031199, 90.7% a.i.) was tested for DNA-damaging properties on rat hepatocytes *in vitro* at concentrations of 0, 0.67 μg/ml, 3.34 μg/ml, 16.69 μg/ml and 83.47 μg/ml (the highest concentration selected was calculated to allow at least 25% cell viability). Two negative controls were used: one containing the vehicle (DMSO) and one untreated. Positive control was diethylnitrosamine at 100 μM. Freshly isolated hepatocytes from a male rat Tif:RAIF(SPF) were cultivated in Williams' medium E containing 10% fetal bovine serum. ^{3}H-thymidine was added to treated and control cultures of rat hepatocytes. Autoradiographs were prepared and 3 slides (50 cells/slide) were scored (silver grains counted) for each treated and control group. No evidence of DNA damage by CGA 64250 technical was found at concentrations up to and including 83.47 μg/ml.

20. BALB/3T3 Cell Transformation Assay

In a cell transformation assay (MRID 00133349) CGA 64250 technical (Batch No. Op. 103119; purity 90.7%) was tested for transformation-inducing properties in mammalian fibroblasts *in vitro* at concentrations of 1.16, 2,31, 4.63, 9.25 and 18.5 μg/ml DMSO. The highest dose level was calculated to produce a 25% reduction in colony-forming ability. Two negative controls were used: 1 untreated and 1 vehicle-treated. Two positive control groups were treated with methylcholanthrene at concentrations of 1.5 or 3.0 μg/ml. Fourteen replicate dishes were used in each of the treated and control groups. Under the conditions of this assay, CGA 64250 did not cause a measurable increase in transformation of BALB/3T3 cells.

21. Tumor Promotion Study - Rats

In an acceptable/non-guideline tumor promotion study (MRID 00151517), newborn Tif:Raif (SPF) rats were injected with 15 mg/kg DENA (ip) dissolved in 0.9% NaCl (140 μmol DENA/kg BW). The control animals were injected ip once with the vehicle alone. At three weeks, pups were weaned and were randomly assigned to 3 separate experimental subgroups of 15 rats/sex. Each of these subgroups was further divided into three subgroups of 5 rats/sex. Individual diets were prepared by combining either phenobarbital at 500 ppm (reference promoter) or 2000 ppm CGA 64250 (batch no. OP.301064, purity 89.7%) with basal diet. The rats were fed respective diets for a period up to 8 weeks. Five pups/sex/group were sacrificed at 2, 4, and 8 weeks after weaning. Liver sections were stained for gamma-glutamyl-transpeptidase (GGT) to determine the focal or diffuse GGT-positive changes.

There was no evidence of clinical signs of toxicity, mortality or adverse effect on body weight. The liver was the only organ considered in the necropsy of the animals. The liver to body weight ratio was found to increase after dosing with phenobarbital or CGA 64250 (with or without pretreatment with DENA) when compared to vehicle control groups of either sex. There were no compound-related effects in gross or histo-pathological examination.

CGA 64250 was found to promote non-neoplastic and neoplastic proliferative rat liver changes when fed to weaned rats for 2, 4, and 8 weeks at 2000 ppm with or without pretreatment with an initiator and the effects were comparable to those produced by 500 ppm of phenobarbital feeding.

E. ABSORPTION AND METABOLISM STUDIES

22. Dermal absorption - Rats

In an acceptable/guideline dermal absorption study (MRID's 42415701, 00164469 & 45345901), groups (4/group) of young adult male, Harlan Sprague-Dawley rats were exposed to aqueous suspension of 3.6EC formulated product of triazole-[3,5-]^{14}C- CGA-64250 at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1 or 1 mg/cm^2, respectively) to a 10 cm^2 shaven dorso-lumbar area. One group of four rats/dose were exposed for 24 hours, while two other groups of four rats each/dose were exposed for 10 or 24 hours followed by a 72-hour depletion phase. This study is an addendum to an earlier study where groups of four male rats each were treated similarly but exposed for 2, 4 or 10 hours (MRID 00164469).

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 57.13, 27.14 and 30.10% of total dose 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. The results of the earlier study (MRID 00164469) demonstrated that 26-35% of the applied radioactivity (at all dose levels) is absorbed within the first two hours and remained fairly constant for the longer exposure periods of 4 and 8 hours except for the low dose of 0.01 mg/cm^2 where it increased to 54%. The average dermal absorption of propiconazole over a 10 hour period at an exposure level of 0.01 mg/cm^2 is approximately 40%.

23. Metabolism Study - Rat

In a metabolism study [MRID 00074506 & 00074507], urinary and fecal metabolites of (U-^{14}C)-phenyl or ^{14}C-triazole ring labeled propiconazole administered (~32 mg/kg) to Tif:RAI F (SPF) male rats were investigated. Within 3 days >95% of the administered triazole labeled dose was excreted in urine (52%) and feces (43%). Animals treated with the phenyl label showed a similar pattern of excretion in urine (51%) and feces (48%).

Examination of the 0-24 hour urine by two dimensional TLC revealed 12 metabolites in both the triazole and phenyl labeled and a 13th metabolite in the triazole labeled compound. No parent material was detected. When the urine was incubated with β-glucurodinase or with β-glucurodinase/aryl sulfatase certain metabolite fractions disappeared suggesting the presence of glucuronic acid and sulfuric acid conjugates. Two other fractions co-chromatographed with CGA 77502 and CGA 58533. High voltage electrophoresis showed 80% of the urinary metabolites to be acidic and fecal metabolites were some what polar.

The percentages of fecal metabolites extracted and distributed at various pH's were not substantially different between the triazole and phenyl labeld CGA 64250. TLC of the fecal extracts revealed at least 8 metabolites, which were less polar than the urinary metabolites. TLC also indicated the presence of metabolites CGA 77502 and CGA 58533 in addition to unchanged parent material (5% of fecal radioactivity).

The similarities in the excretion pattern and metabolite distribution from the two different lables suggest that the bridge between the phenyl ring and the triazole ring remained intact. The proposed major metabolic pathway appears to involve the cleavage of the dioxalone ring with subsequent dechlorination and conjugation and through the oxidation of the propyl side chain. The metabolic profile of both urine and feces appear to be similar except for the presence of parent material in the feces while the urine had conjugated phenolic metabolites.

24. Metabolism Study - Rat

In an acceptable/guideline metabolism study [MRID 41326701], the absorption, distribution, metabolism and excretion of propiconazole labeled with (U-^{14}C)-Phenyl was investigated in groups of (5/sex/group) Sprague-Dawley rats (Crl:CD(SD)BR strain) following oral or intravenous (iv) administration at dose levels of 0.5 mg/kg. Additionally, one group was administered daily single oral dose of 0.5 mg/kg of the non-radiolabeled compound for 14 days followed with a single oral dose of 0.5 mg/kg of the radiolabeled material 24 hours after the last dose. Another group was administered a single oral dose of 50 mg/kg of the radiolabeled compound.

Administration of 0.5 mg/kg of radiolabeled CGA 64250 to rats by oral or iv routes resulted in similar patterns of elimination, possibly as a result of biliary excretion. Renal elimination data suggest that 35-50% of the oral dose was absorbed. More than 90% of the administered radioactivity was eliminated in the urine and feces (including cage washes) after 168 hours of dosing. Most of the excreted radioactivity occurred within the first 48 hours of treatment. Traces or non detectable levels were seen in the tissues and expired air. Female rats appeared to eliminate more of the radioactivity in the urine than in the feces(46.3% vs 39.0% in the orally dosed; 43.8% vs 37.0% in the iv dosed). While male rats eliminated more radioactivity in the urine than in the feces in most of the groups except for the iv group where urine and fecal elimination were about equal. No significant differences in the excretion pattern were seen between the low and high oral dose groups or the repeated dosing group. The distribution of

radioactivity in tissues was similar in low and high dose groups.

Examination of the pooled urine and fecal samples indicated that (U-^{14}C)-Phenyl labeled CGA 64250 was extensively metabolized. The proposed metabolic pathway involves initial side chain oxidation giving the hydroxylated propyl derivative or replacement of the propyl group by carboxylic acid. The alkyl side chain attached to the dioxolane ring in CGA 64250 is probably attacked with the possible loss of the dioxolane ring itself. The radiolabled parent compound was only detected in the urine of the iv group males and females (27.1 and 29.9% of the urine radioactivity in males and females, respectively). In the feces, no parent material was detected in the iv group, but detected in the other groups (6.8-17.6% of the fecal radioactivity in males and females). Most of the fecal radioactivity was not characterized.

25. Metabolism Study - Rat

In a metabolism study [MRID 42403901], the metabolism and excretion of propiconazole labeled with ^{14}C at the triazole-[3,5] position was investigated in TIF: RIA f (SPF) male rats orally gavaged a single dose of 31.4 mg/kg.

The test compound was rapidly metabolized with 81, 94 and 96% of the radioactivity appearing in the urine and feces 1,2, and 3 days, respectively after dosing. The ratio of the urine to feces radioactivity was approximately 5:4. The parent compound is extensively metabolized; only a small percentage remained unabsorbed and appeared in the feces. The n-propyl side chain is first metabolized to α-, β- and γ-hydroxy derivatives and then to α,β- and β,γ- diols. The α, β- diol is further metabolized to α-hydroxy carboxylic derivative, a major metabolite (11%) in the urine. The side chain is sequentially decarboxylated to yield acetic and formic acid derivatives. Once the dioxolane derivative ring is cleaved, a wide variety of metabolic reactions occurs, leading, in general, to the hydroxylation of the dichlorophenyl and triazole rings. Sulfation appeared to be the preferential route of secondary metabolism and accounted for 5.5% of the dose.

26. Metabolism Study - Rat and Mouse

In an acceptable/guideline metabolism study [MRID 00164795], the absorption, distribution, metabolism and excretion of (U-^{14}C)-phenyl labeled propiconazole was investigated in CD-1 mice and Tif:RAI F (SPF) rats. Male and female mice (5/dose level) were fed ad libitum unlabeled CGA 64250 (Batch No. OP 412127, 91.1% purity) in the diet for 21 days at levels of 5, 100 or 2500 ppm followed by a single oral dose of the radiolabeled CGA 64250 (Batch No. GAN-VA-43) at the corresponding levels (equivalent to 0.81, 16.8 and 434 mg/kg for males and 1.02, 21.5 and 475 mg/kg for the females). Three female mice were given a bolus dose of 600 mg/kg ^{14}C-CGA 64250 without pretreatment of unlabeled compound (these mice showed severe signs of toxicity and two died 48-72 hours post dosing). Two male rats were given 9.4 mg/kg single oral dose of the ^{14}C-CGA 64250 without pretreatment of unlabeled compound.

Mice pre-treated with the unlabeled CGA 64250 excreted 83-103% of the administered ^{14}C

radioactivity within 96 hours (mostly within the first 24-48 hours) in the urine and feces. The high dose females excreted the least amount (83% of the administered dose (AD). More radioactivity (particularly at the higher doses of 100 and 2500 ppm) was excreted in the urine than in the feces (1.5-3.7x) in males and females. Total recovered radioactivity ranged from 88-106% of the AD. The male rats excreted nearly equal amounts of the radioactivity in urine (48%) and feces (54%). Tissues and carcass residues were less than 0.55% of the AD in treated rats and mice. Four days post dosing with ^{14}C-CGA 64250, residues were detected in the liver in rats and liver, kidneys and carcass in mice.

Two dimensional TLC revealed 15-30 metabolites in the 0-24 urine samples (identified in the report by their TLC code as U_1, U_2, U_9, U_{12}, U_{17}, U_{18} representing 5-19%, 6-73%, 2-8%, 2-22%, 2-3% and 1-16% of the urine radioactivity. Metabolite U_2 was highest in the male mice urine (61-73%). Female mice urine contained 29-36% while the male rat had the least (6%) of the U_2 metabolite. The U_{12} fraction was another example of species and sex difference in metabolic products. At 5 and 100 ppm female mice (and the male rats) excreted more of the U_{12} metabolite than in the other groups (18 and 21% in female mice, respectively and 22% in male rats). In an earlier study this metabolite was identified as α-hydroxy-carboxyacid (metabolite CU).

When mouse urine was incubated with β-glucuronidase then 75-85% of the U_2 fraction disappears giving rise to a more unpolar U_{18} fraction. In rat urine, however, the most polar fraction U_1 completely disappears after β-glucuronidase incubation and forms several unpolar fractions while the U_2 fraction of the rat urine is not significantly affected. The U_{18} fraction consisted of at least two compounds, one is the alcohol CGA 91305 and the other is the analogus ketone CGA 91304. The major urinary metabolite isolated from the U_2 fraction was determined to be Met IU, the glucuronic acid conjugate of metabolite CGA 91305.

It was concluded that the major metabolic pathway in mice proceeds via elimination of the dioxolane ring leading via ketone formation (CGA 91304) to the corresponding acid to yield metabolite CGA 91305. In males this represents 30% of the AD whereas in the females it represents 15% of the AD. In rats, the non-polar metabolite fractions U_{15} through U_{18} represent metabolites where the dioxolane ring has been cleaved. In conclusion mice cleared the dioxolane ring to a greater extent (70 & and 40% for males and females, respectively) than do male rats (30%).

F. ACUTE TOXICITY STUDIES

27. Acute Oral Toxicity - Rabbit

In an acceptable/guideline acute oral toxicity study (MRID 00058594) rabbits (6/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) in polyethylene glycol 400 at 0, 600, 1000, 2150 or 3590 mg/kg. The rabbits were observed at regular intervals for 14 days for signs of toxicity and mortality.

The LD_{50} was 1344 (1062-1710) mg/kg for both sexes (Toxicity Category III).

28. Acute Oral Toxicity - Chinese Hamster

In an acceptable/guideline acute oral toxicity study (MRID 00058593) Chinese hamsters (5/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) in polyethylene glycol 400 at 1000, 3000, 4500 or 6000 mg/kg. The hamsters were observed at regular intervals for 14 days for signs of toxicity and mortality.

The LD_{50} was 3006 (2152-3943) mg/kg for both sexes (Toxicity Category III).

29. Acute Oral Toxicity - Mouse

In an acceptable/guideline oral toxicity study (MRID 00058592) Tif:MAG (SPF) 5/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) at 800, 1500, 2500 or 3000 mg/kg. The mice were observed at regular intervals for 14 days for signs of toxicity and mortality.

The LD_{50} was 1490 (1138-1875) mg/kg for both sexes (Toxicity Category III.

30. Acute Oral Toxicity - Rat

In an acceptable/guideline acute oral toxicity study (MRID 00058591 & 93194026) healthy random bred Tif:Raif (SPF) rats (5/sex/dose) were administered (by gavage) single oral doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) at 500, 1000, 3000 or 4000 mg/kg. The rats were observed at regular intervals for 14 days for signs of toxicity and mortality.

The LD_{50} was 1517 (958-2291) mg/kg for both sexes. CGA 64250 was placed in Toxicity Category III).

31. Primary Eye Irritation

In an acceptable/guideline primary eye irritation study [MRID 00058597 & 93194029], 0.1 ml of technical CGA 64250 (purity 93.0%, batch no. IN 13/5) was instilled into the lower conjunctival sac of the left eye of each of six rabbits. The right eye of each rabbit remained untreated and served as the untreated control. In 3 of 6 rabbits approximately 30 seconds after each treatment, the treated eye was flushed with 10 ml of physiological saline. The eye irritation was appraised with a slit lamp on day 1, 2, 3, 4 and 7 and scored according to Draize method.

In the unwashed eyes chemosis, discharge and redness cleared in all animals at 48 hours; the P.I. was 2.4/110 and the corneal opacity in 2/3 eyes and was reversible within 72 hours. Average irritation scores were 8.7, 3.3 and 0.0 at 24, 48 and 72 hours, respectively.

In the washed eyes the P.I. was 0.4/110 and no corneal opacity. Conjunctivitis was reversible within 48 hours. Average irritation scores were 2.0, 0.0 and 0.0 at the 24, 48 and 72 hours, respectively.

CGA 64250 technical is a moderate eye irritant. It is placed in TOXICITY CATEGORY III for primary eye irritation based on corneal opacity which was reversible within 72 hours.

32. Primary Dermal Irritation

In an acceptable/guideline primary dermal irritation study (MRID 00058598 & 93194030), 0.5 ml of technical CGA 64250 (93.0 % purity, Batch IN 13/5) was applied to the intact and abraded skin of 3 male and 3 female adult Himalayan rabbits under an impervious cuff for 24 hours. The test sites were examined and graded for irritation at 1, 2, 3,4, and days.

Slight erythema and edema which lasted in 3 rabbits up to 4 days was noted. No irritation at day 7 was reported.

For intact/non-abraded sites, dermal irritation scores after 1, 2, 3, 4 and 7 days averaged 2.15, 1.5, 0.95, 0.0, and 0.0, respectively. For abraded sites, dermal irritation scores after 1, 2, 3, 4 and 7 days averaged 2.5, 1.8, 1.15, 0.80, and 0.0, respectively.

The irritation index (P.I.) is 1.4. CGA was placed in Toxicity Category IV for dermal irritation.

33. Acute Dermal Toxicity - Rat

In an acceptable/guideline acute dermal toxicity study (MRID 00058596 & 93194027) Tif:Raif (SPF) rats (5/sex/dose) received single dermal applications of technical CGA 64250 (93.0 % purity, Batch IN 13/5) on the intact skin of the fur-clipped trunk (approximately 60 cm^2) under an impervious cuff for 24 hours at 3000 or 4000 mg/kg. No vehicle was used and a vehicle control was not necessary. Abraded skin was not tested.

The LD_{50} was >4000 mg/kg for both sexes. CGA 64250 was placed in dermal Toxicity Category III.

34. Skin Sensitization - Guinea Pigs

In an acceptable/guideline dermal sensitization study (MRID 00058600 & 93194031) with technical CGA 64250 (93.0 % purity, Batch IN 13/5), adult male Pirbright Guinea pigs using the Maurer optimization test were tested. The test was performed on groups of 10 male and 10 female guinea pigs, one control group (20 animals) and one experimental group (20 animals). During the induction period the animals received one injection on alternate days (except weekends) to a total of 10 intracutaneous injections of a freshly prepared 0.1% dilution of CGA 64250 in propylene glycol. One control group was treated with the vehicle alone. Fourteen days

after the last sensitizing injection, an intracutaneous challenge injection of 0.1 ml of a freshly prepared 0.1% dilution of CGA 64250 in propylene glycol was administered into the skin of the left flank. Twenty four hours after each injection during the first week of the induction period and 24 hours after the challenge injection the reactions were scored. Ten days after the intracutaneous challenge injection a sub-irritant dose of the test compound was applied epicutaneously under occlusive dressing which was left in place for 24 hours.

Under the experimental conditions employed, no differences between the test group and the vehicle treated controls were seen, after either epidermal or intradermal challenge application of CGA 64250. It was concluded that CGA 64250 technical is not a skin sensitizer (contact allergen) in albino guinea pigs.

Supplement to HED Document No. 000789 - DER for MRID 00058600 and MRID 93194031: CGA 64250 Technical - Skin Sensitization Study - Guinea Pigs. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Skin Sensitization Study - Guinea Pigs; OPPTS 870.2600 [§81-6]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (viscous brown liquid, 93.0% purity)

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

CITATION: Ulmann, L. 1979. Report on the Skin Sensitizing (Contact Allergenic) Effect in Guinea Pigs of Technical CGA 64250, Project No. 785250, Ciba-Geigy Ltd, Switzerland. February 8 , 1979. MRID 00058600 Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058600. Skin Sensitization in the Guinea Pig: Propiconazole: Study # 785250. Prepared by Ciba- Geigy Ltd., July 10, 1990. MRID 93194031. Unpublished

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a dermal sensitization study (MRID 00058600 & 93194031) with technical CGA 64250 (93.0 % purity, Batch IN 13/5), adult male Pirbright Guinea pigs using the Maurer optimization test were tested. The test was performed on groups of 10 male and 10

female guinea pigs, one control group (20 animals) and one experimental group (20 animals). During the induction period the animals received one injection on alternate days (except weekends) to a total of 10 intracutaneous injections of a freshly prepared 0.1% dilution of CGA 64250 in propylene glycol. One control group was treated with the vehicle alone.

Fourteen days after the last sensitizing injection, an intracutaneous challenge injection of 0.1 ml of a freshly prepared 0.1% dilution of CGA 64250 in propylene glycol was administered into the skin of the left flank.

Twenty four hours after each injection during the first week of the induction period and 24 hours after the challenge injection the reactions were scored. Ten days after the intracutaneous challenge injection a sub-irritant dose of the test compound was applied epicutaneously under occlusive dressing which was left in place for 24 hours.

Under the experimental conditions employed, no differences between the test group and the vehicle treated controls were seen, after either epidermal or intradermal challenge application of CGA 64250.

It was concluded that CGA 64250 technical is not a skin sensitizer (contact allergen) in albino guinea pigs.

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.2600 [§81-6] for a dermal sensitization study in the Guinea pig.

COMPLIANCE: This study predated the GLP Guidelines. A phase 3 summary (MRID 93194031) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

Supplement to HED Document No. 000789 - DER for MRID 00058596 and MRID 93194027: CGA 64250 Technical - Acute Dermal Toxicity Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity Study - Rat; OPPTS 870.1200 [§81-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (viscous brown liquid, 93.0% purity)

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

CITATION: Bathe, R. 1979. Report on Acute Dermal LD_{50} in the rat of Technical CGA 64250 Project No. 785245. Ciba-Geigy Ltd, Switzerland. June 22, 1979. MRID. 00058596 Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 58596. Acute Dermal Toxicity in the Rat: Propiconazole: Study # 785245. Prepared by Ciba-Geigy Ltd., July 10, 1990. MRID No. 93194027. Unpublished

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In an acute dermal toxicity study (MRID 00058596 & 93194027) Tif:Raif (SPF) rats (5/sex/dose) received single dermal applications of technical CGA 64250 (93.0 % purity, Batch IN 13/5) on the intact skin of the fur-clipped trunk (approximately 60 cm^2) under an impervious cuff for 24 hours at 3000 or 4000

mg/kg. No vehicle was used and a vehicle control was not necessary. Abraded skin was not tested.

None of the animals exhibited toxicologic effects during the first 24 hours of treatment. Toxic signs in the subsequent 8 days reported were dyspnea, ruffled fur and curved body position. All animals appeared normal on the 9th day of treatment. There were no deaths reported and rats gained weight. Necropsy findings of individual animals were unremarkable.

The LD_{50} was >4000 mg/kg for both sexes. CGA 64250 was placed in dermal Toxicity Category III.

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.1200 [§81-2] for an acute dermal toxicity in rats.

COMPLIANCE: This study predated the GLP Guidelines. A phase 3 summary (MRID 93194027) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

Supplement to HED Document No. 000789 - DER for MRID No.00058594: CGA 64250 Technical - Acute Oral Toxicity Study - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan, Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity Study - Rabbit; OPPTS 870.1100 [§81-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (93.0% purity, viscous brown liquid)

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

CITATION: Sachsse, K; Ulmann, L. 1978. Acute Oral LD_{50} in the Rabbit of Technical CGA 64250 Project No. 785247, Ciba-Geigy Ltd, Switzerland. November 2, 1978. MRID. 00058594 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In an acute oral toxicity study (MRID 00058594) rabbits (6/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) in polyethylene glycol 400 at 0, 600, 1000, 2150 or 3590 mg/kg. The rabbits were observed at regular intervals for 14 days for signs of toxicity and mortality.

Toxic signs reported were sedation, dyspnea, ruffled fur, curved body position, tremors, convulsions, ataxia. Survivors gained weight. No gross pathology was seen.

All animals in the 2150 and 3590 mg/kg groups died within the

first 2 days of treatment. All animals in the control and low dose group (600 mg/kg) survived the treatment. Mortality in the 1000 mg/kg groups was 33% for males and 0% for females.

The LD_{50} was 1344 (1062-1710) mg/kg for both sexes (Toxicity Category III).

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.1100 [§81-1] for an acute oral toxicity in rabbits.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No.00058593: CGA 64250 Technical - Acute Oral Toxicity Study - Chinese Hamster. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity Study - Chinese Hamster; OPPTS 870.1100 [§81-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (93.0% purity, viscous brown liquid)

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

CITATION: Bathe, R. 1979. Report on Acute Oral LD_{50} in the Chinese Hamster of Technical CGA 64250 Project No. 790146, Ciba-Geigy Ltd, Switzerland. April 20, 1979. MRID. 00058593 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In an acute oral toxicity study (MRID 00058593) Chinese hamsters (5/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) in polyethylene glycol 400 at 1000, 3000, 4500 or 6000 mg/kg. The hamsters were observed at regular intervals for 14 days for signs of toxicity and mortality.

Toxic signs reported were sedation, dyspnea, exopthalmos ruffled fur, curved body position in all groups and persisted for up to 11 days. Surviving animals recovered after 11-12 days of treatment. Survivors gained weight. No gross pathology was seen.

All animals in the high dose group died within the first 3 days of treatment. All animals in the low dose group (1000 mg/kg) survived the treatment. Mortality in the 3000 and 4500 mg/kg groups was 40 and 60% for males and 60 and 80% for females, respectively. Mortalities occurred within the first 4 days of treatment.

The LD_{50} was 3006 (2152-3943) mg/kg for both sexes (Toxicity Category III).

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.1100 [§81-1] for an acute oral toxicity in hamsters.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No.00058592: CGA 64250 Technical - Acute Oral Toxicity Study - Mouse. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity Study - Mouse; OPPTS 870.1100 [§81-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (93.0% purity, viscous brown liquid)

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

CITATION: Bathe, R. 1979. Report on Acute Oral LD_{50} in the Mouse of Technical CGA 64250 Project No. 785243, Ciba-Geigy Ltd, Switzerland. May 7, 1979. MRID. 00058592 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In an acute oral toxicity study (MRID 00058592) Tif:MAG (SPF) mice (5/sex/dose) were administered single oral (by gavage) doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) at 800, 1500, 2500 or 3000 mg/kg. The mice were observed at regular intervals for 14 days for signs of toxicity and mortality.

Toxic signs were observed on the first day of dosing and included sedation, dyspnea, ruffled fur, ventral, lateral or curved body position in all animals in all groups and persisted for up to 10 days. Surviving animals recovered after 10-11 days of treatment. Survivors gained weight. No gross pathology was seen.

All animals in the high dose group and all females in the 2500 mg/kg group died within the first 3 days of treatment. 80% of the males in the 1500 and 2500 groups died within the first 4 days of treatment. Females in the 1500 mg/kg survived. Mortality in the 800 mg/kg group was 0 for males and 20% for females.

The LD_{50} was 1490 (1138-1875) mg/kg for both sexes (Toxicity Category III).

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.1100 [§81-1] for an acute oral toxicity in mice.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No. 00058591 and MRID 93194026: CGA 64250 Technical - Acute Oral Toxicity Study - Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity Study - Rat; OPPTS 870.1100 [§81-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical (93.0% purity, viscous brown liquid)

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

CITATION: Bathe, R. 1978. Report on Acute Oral LD_{50} in the rat of Technical CGA 64250 Project No. 785244, Ciba-Geigy Ltd, Switzerland. December 7, 1978. MRID. 00058591 Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058591. Acute Inhalation Toxicity in the Rat. Study No. 785244. Prepared by Ciba- Geigy Ltd., July 10, 1990. MRID No. 93194026. Unpublished

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In an acute oral toxicity study (MRID 00058591 & 93194026) healthy random bred Tif:Raif (SPF) rats (5/sex/dose) were administered (by gavage) single oral doses of technical CGA 64250 (93.0% purity, batch no. IN 13/5) at 500, 1000, 3000 or 4000 mg/kg. The rats were observed at regular intervals for 14 days for signs of toxicity and mortality.

Toxic signs were observed on the first day of dosing and included sedation, dyspnea, ruffled fur, piloerection, ventral, lateral or curved body position in all animals in all groups. Dyspnea, piloerection, curved body position persisted for 14 days. Survivors gained weight.

All animals in the high dose group died within the first 7 days of treatment. Deaths also occurred in the 1000 and 3000 mg/kg group. No deaths occurred in the 500 mg/kg group.

A gross necropsy examination was conducted on each animal which died during the study and each animal which survived through termination of study. No gross pathology related to treatment was reported.

The LD_{50} was 1517 (958-2291) mg/kg for both sexes. CGA 64250 was placed in Toxicity Category III).

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.1100 [§81-1] for an acute oral toxicity in rats.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No. 00058597 and MRID 93194029: CGA 64250 Technical - eye Irritation - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbits
OPPTS 870.2400 [§81-4]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical (93.0% purity, viscous brown liquid)

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

CITATION: Sachsee, K; Ullmann, L. 1978. Eye Irritation in the Rabbit after Single Application of Technical CGA 64250 Project No. 785248, Ciba-Geigy Ltd, Switzerland. October 26, 1978. MRID 00058597 Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058597. Primary eye Irritation in Rabbit: Propiconazole: Study # 785248. Prepared by Ciba-Geigy Ltd., July 10, 1990. MRID No. 93194029. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a primary eye irritation study [MRID 00058597 & 93194029], 0.1 ml of technical CGA 64250 (purity 93.0%, batch no. IN 13/5) was instilled into the lower conjunctival sac of the left eye of each of six rabbits. The right eye of each rabbit remained untreated

and served as the untreated control. In 3 of 6 rabbits approximately 30 seconds after each treatment, the treated eye was flushed with 10 ml of physiological saline. The eye irritation was appraised with a slit lamp on day 1, 2, 3, 4 and 7 and scored according to Draize method.

In the unwashed eyes chemosis, discharge and redness cleared in all animals at 48 hours; the P.I. was 2.4/110 and the corneal opacity in 2/3 eyes and was reversible within 72 hours. Average irritation scores were 8.7, 3.3 and 0.0 at 24, 48 and 72 hours, respectively.

In the washed eyes the P.I. was 0.4/110 and no corneal opacity. Conjunctivitis was reversible within 48 hours. Average irritation scores were 2.0, 0.0 and 0.0 at the 24, 48 and 72 hours, respectively.

In this study, CGA 64250 technical is a moderate eye irritant. It is placed in TOXICITY CATEGORY III for primary eye irritation based on corneal opacity which was reversible within 72 hours.

This study is classified as **Acceptable** and satisfies the guideline requirement for a primary eye irritation study OPPTS 870.2400 [§81-4] in the rabbit.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID 00058598 and MRID 93194030: CGA 64250 Technical - Skin Irritation Study - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation Study - Rabbit; OPPTS 870.2500 [§81-5]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (93.0% purity, viscous brown liquid)

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

CITATION: Sachsse, K; Ulmann, L. 1978. Skin Irritation in the Rabbit after Single Application of Technical CGA 64250, Project No. 785249, Ciba-Geigy Ltd, Switzerland. October 29, 1978. MRID 00058598 Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058598. Primary Dermal Irritation in the Rabbit: Propiconazole: Study # 785249. Prepared by Ciba- Geigy Ltd., July 10, 1990. MRID No. 93194030. Unpublished

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a primary dermal irritation study (MRID 00058598 & 93194030), 0.5 ml of technical CGA 64250 (93.0 % purity, Batch IN 13/5) was applied to the intact and abraded skin of 3 male and 3 female adult Himalayan rabbits under an impervious cuff for 24 hours.

The test sites were examined and graded for irritation at 1, 2, 3,4, and days.

Slight erythema and edema which lasted in 3 rabbits up to 4 days was noted. No irritation at day 7 was reported.

For intact/non-abraded sites, dermal irritation scores after 1, 2, 3, 4 and 7 days averaged 2.15, 1.5, 0.95, 0.0, and 0.0, respectively. For abraded sites, dermal irritation scores after 1, 2, 3, 4 and 7 days averaged 2.5, 1.8, 1.15, 0.80, and 0.0, respectively.

The irritation index (P.I.) is 1.4. CGA was placed in Toxicity Category IV for dermal irritation.

The study was classified **Acceptable** and it meets the Guideline requirements OPPTS 870.2500 [§81-5] for an acute dermal irritation study in rabbits.

COMPLIANCE: This study predated the GLP Guidelines. A phase 3 summary (MRID 93194030) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

Supplement to HED Document No. 000789 - DER for MRID No. 00058601: CGA 64250 Technical - Salmonella/Mammalian Microsome Mutagenicity Test. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan, Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - Bacterial Reverse Mutation Test; OPPTS 870.5100 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (Purity not specified)

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

CITATION: Arni, P.; Muller, D. 1979. Salmonella/Mammalian Microsome Mutagenicity Test with CGA 64250, Project No. 792577, Ciba-Geigy Ltd, Switzerland. September 17, 1979. MRID No. 00058601 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a plate incorporation assay (MRID No. 00058601), *Salmonella typhimurim* strains TA-98, TA-100, TA-1535. TA-1537 were exposed to CGA 64250 (Batch No. Jn 18/5 F 1-2; purity not specified) at 25, 75, 115, 675 or 2025 µg/plate, both in the presence and absence of a rat microsomal activation system. Positive controls were tested.

No mutagenic effect was noted with or without microsomal activation at the various concentrations of CGA 64250.

The study was originally classified **Acceptable**. However the test material purity was not specified in the report nor the test material was tested at high enough concentration of 5000

µg/plate or up to a cytotoxic dose. Therefore the study is considered **Unacceptable** and does not meet the Guideline requirements OPPTS 870.5100 [§84-2] for a bacterial reverse mutation assay.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 004276 & 005352 - DER for MRID 00133343: CGA 64250 Technical -Saccharomyces Mutagenicity Assay. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-21-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - Mitotic Gene Conversion in *Saccharomyces cerevisiae* Assay; OPPTS 870.5575 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (90.7%)

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

CITATION: Arni, P. 1982. *Saccharomyces cerevisiae* D7/mammalain-microsome Mutagenicity Test *in vitro* with CGA 64250. Project No. 811558, Ciba-Geigy Ltd, Switzerland. August 19, 1982. MRID 00133343. Unpublished.

151505 Arni, P. (1985) Saccharomyces cerevisae D7/Mammalian-Microsome Mutagenicity Test in vitro: CGA 64250: Supplement to the Report Dated August 19, 1982: Test No. 811558. Unpublished study prepared by Ciba-Geigy Ltd. 5 p.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a mitotic gene conversion assay (MRID 00133343) CGA 64250 technical (Batch No. Op. 103119; purity 90.7%) was tested for mutagenic properties in yeast cells using the D7 strain of *Saccharomyces cerevisiae*. The tests were performed with and without activation (rat liver microsomes and cofactor) at CGA 64250 concentrations of 0 (DMSO as control), 10, 30, 90, or 270

µg/ml. Positive control was 4-nitroquinoline-N-oxide at 0.2 µg/ml (without microsomal activation) and cyclophosphamide at 300 µg/ml (with microsomal activation).

An inhibitory effect on the growth of yeast cells especially at concentrations of 30, 90 and 270 µg/ml was noted. There was no increase in adenine dependent cells, convertants or revertnats indicating that the test material did not induce mutation. However the study was classified **Unacceptable** pending data on individual plate counts and a table of statistics for the assay with microsomal activation. The additional data were submitted by the registrant and found to be satisfactory by HED (HED Doc. No. 005352). The study was **upgraded to Acceptable** and it does meet the Guideline requirements OPPTS 870.5575 [§84-2] for a mitotic gene conversion in *Saccharomyces cerevisiae* assay. It was concluded that under the experimental conditions of the this study, CGA 64250 technical did not induce mutation in *Saccharomyces cerevisiae* cells with or without metabolic activation (rat liver S-9 mix.).

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No. 00058603: CGA 64250 Technical - Bone Marrow Chromosomal Aberration Test - Hamster. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - Bone Marrow Chromosomal Aberration Test - Hamster; OPPTS 870.5385 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (90.0%)

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

CITATION: Hool, G.; Langauer, M. 1979. Nucleus Anomaly Test in Somatic Interphase nuclei with CGA 64250 in the Chinese Hamsters, Project No. 790805, Ciba-Geigy Ltd, Switzerland. September 17, 1979. MRID. 00058603 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a micronucleus anomaly test (MRID No. 00058603), propiconazole as CGA 64250 (Batch INA 35/1 P1, purity 90.0%) was administered by gavage at dosages of 251, 502 or 1004 mg/kg in 20 ml/kg PEG 400 to groups of 6 male and 6 female Chinese hamsters each. Treatment consisted of one daily application on 2 consecutive days. The animals were sacrificed 24 hours after the second application. Smears were made from the bone marrow.

One male animal from the highest dose group died after the second application.

Bone marrow smears from animals treated with CGA 64250 showed no

significant difference from the control. By contrast, a positive control experiment with cyclophosphamide (128 mg/kg) yielded 8.92% cells with anomalies of nuclei. This is significantly different from the controls treated with the vehicle (PEG 400) alone. No evidence of mutagenic effects was obtained in Chinese hamsters treated with CGA 64250.

The study is classified **Acceptable/Guideline** and meets the Guideline requirements for a chromosomal aberration assay (OPPTS 870.5385; [§84-2]).

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 000789 - DER for MRID No.00058602: CGA 64250 Technical - Dominant Lethal Assay - Mouse. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Dominant Lethal Assay - Mouse; OPPTS 870.5450 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (90.0%)

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

CITATION: Hool, G. 1979. Dominant Lethal Study with CGA 64250 in the Mouse, Project No. 790034, Ciba-Geigy Ltd, Switzerland. October 31, 1979. MRID 00058602 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a dominant lethal study (MRID No 00058602), propiconazole as CGA 64250 (Batch INA 35/1 P1, purity 90.0%) was administered by oral gavage as single doses of 165 or 495 mg/kg to groups of 20 male albino mice Tif:MAG F (SPF) which were then each mated to two untreated females from the same strain over a period of 6 weeks. At the end of each week the females were replaced by new ones.

Males in the high dose group showed some toxic reactions to the treatment. Six of the 20 animals showed ventral position and dyspnea, recovering at least after two days except for one animal that developed eczema and was unable to mate and was sacrificed in the fourth mating period.

Females mated to CGA 64250 treated males did not differ significantly from the females mated to controls, in mating ratio, the number of implantations and embryonic deaths (resorption). Pregnancy rates of females mated to the treated males were comparable to the females mated to controls. It was concluded that no evidence of dominant lethal effects was observed in the progeny of male mice treated with CGA 64250.

The study is classified **Acceptable/Guideline** and meets the Guideline requirements for a dominant lethal assay (OPPTS 870.5450 [§84-2]).

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 004276 - DER for MRID No. 00133347 and HED 005352 for MRID 00151508: CGA 64250 Technical -DNA Test on Human Fibroblasts. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - Unscheduled DNA Synthesis in Mammalian Cells; OPPTS 870.5550 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (purity 90.7% a.i.)

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

CITATION: Puri, E. 1982. Autoradiographic DNA Repair Test on Human Fibroblasts: CGA 64250 (*in vitro* Test for DNA-damaging Properties). Project No. 811655, Ciba-Geigy Ltd, Switzerland. August 12, 1982. MRID 00133347. Unpublished.

Puri, E. (1985) Autoradiographic DNA Repair Test on Human Fibro-blasts: CGA 64250: Supplement to the Report Dated August 12,1982: Test No. 811655. MRID 00151508. Unpublished study prepared by Ciba-Geigy Ltd. 10 p.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a unscheduled DNA assay (MRID 00133347, 00151508) CGA 64250 technical (Batch No. Op. 103119, 90.7% a.i.) was tested for DNA-damaging properties on human fibroblasts *in vitro*. Cytotoxicity test was performed to provide a basis for selection of the test substance concentration range. The highest concentration selected was calculated to allow at least 25% cell viability as

determined by vital staining technique. The experiment was conducted using concentrations of 0, 0.0768, 0.384, 1.92, and 9.60 nl/ml (0, 0.07 µg/ml, 0.37 µg/ml, 1.86 µg/ml and 9.32 µg/ml, respectively). Two negative controls were used: one containing the vehicle and one untreated. Positive control was 4-nitroquinoline-N-oxide (5 µM). ^{3}H-thymidine was added to treated and control cultures of human fibroblasts. Autoradiographs were prepared and 4 slides (50 cells/slide) were scored (silver grains counted) for each treated and control group. Mean values were reported in the original report of the study.

No evidence of CGA 64250 technical induced DNA damage was found at concentrations up to and including 9.32 µg/ml (9.60 nl/ml). The study was initially classified **Unacceptable** due to incomplete reporting. However, the required data was submitted by the registrant (MRID No. 00151508) and found satisfactory (HED Doc. No. 005352). The study was **upgraded to Acceptable** and it does meet the Guideline requirements OPPTS 870.5550 [§84-2] for unscheduled DNA synthesis in mammalian cells.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 004276 - DER for MRID No.00133348 and HED 005352 for MRID 00151509; and MRID 93194044: CGA 64250 Technical -DNA Test on Rat Hepatocytes. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - Unscheduled DNA Synthesis in Mammalian Cells; OPPTS 870.5550 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (purity 90.7% a.i.)

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

CITATION: Puri, E. 1982. Autoradiographic DNA Repair Test on Rat Hepatocytes: CGA 64250 (*in vitro* Test for DNA-damaging Properties). Project No. 811514, Ciba-Geigy Ltd, Switzerland. August 12, 1982. MRID 00133348. Unpublished.

Puri, E. (1985) Autoradiographic DNA Repair Test on Rat Hepato: cytes: CGA 64250: Supplement to the Report Dated August 12, 1982: Test No. 811514. MRID 00151509 Unpublished study prepared by Ciba-Geigy Ltd. 12 p.

Breckenridge, C. (1990) Ciba-Geigy Corp. Phase 3 Summary of MRID 00133348 and Related MRIDs 00151509. DNA Repair Test, Rat Hepatocytes: Propiconazole: Study # 811514. MRID 93194044 Prepared by CIBA-GEIGY Limited. 12 p.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a unscheduled DNA assay (MRIDs 00133348, 00151509 & 93194044) CGA 64250 technical (Batch No. Op. 1031199, 90.7% a.i.) was tested for DNA-damaging properties on rat hepatocytes *in vitro*. Cytotoxicity tests were performed to provide a basis for selection of the test substance concentration range. The highest concentration selected was calculated to allow at least 25% cell viability. The experiment was conducted using concentrations of 0, 0.69, 3.44, 17.2, and 86.0 nl/ml (0, 0.67 µg/ml, 3.34 µg/ml, 16.69 µg/ml and 83.47 µg/ml, respectively). Two negative controls were used: one containing the vehicle (DMSO) and one untreated. Positive control was diethylnitrosamine at 100 µM. Freshly isolated hepatocytes from a male rat Tif:RAIF(SPF) were cultivated in Williams' medium E containing 10% fetal bovine serum.

^{3}H-thymidine was added to treated and control cultures of rat hepatocytes. Autoradiographs were prepared and 3 slides (50 cells/slide) were scored (silver grains counted) for each treated and control group.

No evidence of DNA damage by CGA 64250 technical was found at concentrations up to and including 83.47 µg/ml (86 nl/ml). The study was initially classified **Unacceptable** due to incomplete reporting. However, the required data were submitted by the registrant (MRID 00151509) and found to be satisfactory (HED Doc. No. 005352). The study was **upgraded to Acceptable** and it does meet the Guideline requirements OPPTS 870.5550 [§84-2] for unscheduled DNA synthesis in mammalian cells.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. 004276 - DER for MRID No. 00133349: CGA 64250 Technical - BALB/3T3 Cell Transformation Assay. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: - BALB/3T3 Cell Transformation Assay; OPPTS 870.5300 [§84-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (90.7%)

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

CITATION: Anonymous. 1982. CGA 64250: BALB/3T3 Cell Transformation Assay Project No. 790806, Ciba-Geigy Ltd, Switzerland. August 10, 1982. MRID. 00133349 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a cell transformation assay (MRID 00133349) CGA 64250 technical (Batch No. Op. 103119; purity 90.7%) was tested for transformation-inducing properties in mammalian fibroblasts *in vitro* at concentrations of 1.16, 2,31, 4.63, 9.25 and 18.5 µg/ml DMSO (1% in Eagle's minimum essential medium containing 10% fetal bovine serum). The highest dose level was calculated to produce a 25% reduction in colony-forming ability, based on a preliminary *in vitro* toxicity test. Two negative controls were used: 1 untreated and 1 vehicle-treated. Two positive control groups were treated with methylcholanthrene at concentrations of 1.5 or 3.0 µg/ml. Fourteen replicate dishes were used in each of the treated and control groups.

Under the conditions of this assay, CGA 64250 did not cause a measurable increase in transformation of BALB/3T3 cells.

The study was classified **Acceptable** and it does meet the Guideline requirements for a cell transformation assay (OPPTS 870.5300 [§84-2]).

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to HED Document No. HED 005352 for MRID 00151517: CGA 64250 - Promotion Study. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

AMENDED DATA EVALUATION RECORD

STUDY TYPE: - Promotion Study - Rats; (non-guideline study)

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250

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

CITATION: Froehlich, E. *et al.* 1984. Promotion Study with CGA 64250: Study on the Influence of CGA 64250 in the Formation of Focal Profilerative Changes in the Rat Liver: GU Exploratory Research Project No. 834015. Submitted by Ciba-Geigy Ltd, Switzerland. October 1, 1984. MRID 00151517 (Accession No. 73929) Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a tumor promotion study (MRID 00151517), newborn Tif:Raif (SPF) rats were injected with 15 mg/kg DENA (ip) dissolved in 0.9% NaCl (140 µmol DENA/kg BW). The control animals were injected ip once with the vehicle alone. At three weeks, pups were weaned and were randomly assigned to 3 separate experimental subgroups of 15 rats/sex. Each of these subgroups was further divided into three subgroups of 5 rats/sex. Individual diets were prepared by combining either phenobarbital at 500 ppm (reference promoter) or 2000 ppm CGA 64250 (batch no. OP.301064, purity 89.7%) with basal diet. The rats were fed respective diets for a period up to 8 weeks. Five pups/sex/group were sacrificed at 2, 4, and 8 weeks after weaning. Liver sections

were stained for gamma-glutamyl-transpeptidase (GGT) to determine the focal or diffuse GGT-positive changes. Crieria to identify GGT-positive changes were: (1) clusters of at least 3 clearly delineated GGT-positive cells in the liver, possibly revealing morphological deviation from normal structure recorded as foci or islands, and (2) diffuse perilobular enzymatic GGT activity. Focal changes that presented histological evidence of neoplastic growth were identified.

There was no evidence of clinical signs of toxicity, mortality or adverse effect on body weight. The liver was the only organ considered in the necropsy of the animals. The liver to body weight ratio was found to increase after dosing with phenobarbital or CGA 64250 (with or without pretreatment with DENA) when compared to vehicle control groups of either sex. There were no compound-related effects in gross or histo-pathological examination.

The study deficiencies noted included lack of general health examination of animals prior to testing, the frequency of diet preparation and lack of results of homogeneity and stability analyses, incomplete statistical data analysis and inconsistencies in food consumption data.

The inability to discriminate between diffuse and GGT-positive activity may have resulted in inaccurate reporting of the actual number of foci. Acetone was the primary preservative used for this study which deviates from the protocol of Rutenburg who preserved liver in 3% glutaraldehyde, 10% aqueous formalin, or a formol-calcium solution for a comparative preservation of tissue for use in the histochemical demonstration of GGT activity. Acetone has been found to dehydrate tissue and extract lipids.

The test material was found to cause proliferative changes in the rat liver similar to phenobarbital, a known liver tumor promoter.

CGA 64250 was found to promote non-neoplastic and neoplastic proliferative rat liver changes when fed to weaned rats for 2, 4, and 8 weeks at 2000 ppm with or without pretreatment with an initiator and the effects were comparable to those produced by 500 ppm of phenobarbital feeding.

The study was classified **Acceptable/non-guideline**. It provides useful information for establishing the mechanism of action for CGA 64250.

COMPLIANCE: This study predated the GLP Guidelines.

Supplement to Document No. 004287 & 005352 - DER for MRID No. 00129570. Oncogenicity Study in Mice. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Feeding - Mouse; OPPTS 870.4200 [§83-2b]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical, (87.2-91.9% purity)

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

CITATION: Hunter, B; Slater, N; Heywood, R; Street, A; Prentice, D; Gibson,W; Gopinath, C. 1982. CGA-64250 Long Term Feeding Study in Mice. Huntingdon Research Centre, England, Study number CBG 196/81827, Ciba-Geigy Ltd. Switzerland. November 4, 1982. MRID 00129570. Unpublished.

Ciba-Geigy Corp. (1985) Response to the EPA Review of the Long-Term Feeding Study in Mice with CGA-64250 Technical: Includes Chemistry Data of Test Material, Details of Diet Preparation, Summary of Incidence of Clinical Signs, and Addendum to Report CBG 196/81827. MRID 00151503 Unpublished compilation. 214 p.

Ciba-Geigy Corp. (1983) CGA-64250: Long-term Feeding Study in Mice: Incidence of Liver Tumors in Males. MRID 00130844. (Unpublished study received Sep 14, 1983 under 100-641; CDL:251237-A)

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00129570 and Related MRIDS 0084153, 00151503

and 00130844. Long-Term Feeding Study in Mice: Propiconazole. Study number CBG 196/81827, Prepared by Ciba- Geigy Ltd., July 3, 1990. MRID No. 93194037. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a 24-month oncogenicity study (MRIDs 00129570, 00151503, 00130844 and 93194037), CGA 64250 technical (Batch No. P4-6, 87.2-91.9% purity) was administered to groups of CD-1 mice (52/sex/dose) in the diet at concentrations of 0, 100, 500, or 2500 ppm (10.0, 49.4, and 344.3 mg/kg/day for males and 10.8, 55.6 and 340.3 mg/kg/day for females, respectively). A satellite group (12 mice/sex/dose) was sacrificed at one year. Diets were prepared weekly. During the first year of the study, the test material was ground directly into basal diet. During the second year, the test substance was dissolved in ethyl acetate prior to incorporation into the diet to improve the homogeneity of the test material in the diet. However, the EPA reviewers questioned the use of the ethyl acetate and its impact on the study. The results of analyses for purity (including identification of all impurities) and stability of the test material in the diet provided later by the registrant were found to be satisfactory (HED doc. No. 005352).

A review of the individual clinical observations revealed no obvious treatment-related in-life signs (HED doc. No. 005352). An increase in mortality was noted in males of the 2500 ppm group during the first 6 months. This finding is considered compound-related. Survival at 104 weeks for the control, 100, 500 and 2500 ppm groups was 46%, 38%, 40%, and 27% for the males and 54%, 63%, 46% and 62% for the females, respectively. However, sufficient number of animals were alive at study termination to assess the carcinogenic potential of the test material.

Sporadic decreases in body weight gain, particularly in the high dose male and female groups were noted. Food consumption was increased in high dose male mice only.

There were no compound-related effects on hematological parameters examined. SGPT and SGOT were significantly increased in high dose males and females at 52 weeks and in high dose males at 100 weeks. SAP was increased in high dose males at week 100. These changes are considered indicative of liver damage. Urinalysis results did not reveal any treatment-related effects.

57

Increased liver weight was noted in high and mid dose males and in high dose females both at interim and terminal sacrifice. There was good correlation between gross and microscopic findings. Enlarged livers containing gross pathological changes were seen in high dose animals. Non-neoplastic changes in high dose males and females consisted of hepatocyte enlargement, vacuolation and fat deposition. Liver histopathology of low and mid dose mice was comparable to those of controls.

Amyloidosis occurred more frequently in treated animals compared to controls, but was not dose-related.

Necropsy observations at the termination of the study indicated a treatment-related increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly) among mid- and high-dose males (150% and 140% of controls, respectively) and in high-dose females (367% of control).

CGA 64250 treatment was associated with early expression of malignant liver cell tumors in male mice. The incidences of malignant (presumably carcinomas) liver tumors at the one year interim sacrifice were 0/11, 0/11 1/11, and 3/9 in the control, low, mid and high dose males, respectively. No liver tumors were found in any of the female mice sacrificed at the 1-year interim sacrifice.

The total incidences of combined liver adenomas/carcinomas in males for the control, 100, 500 and 2500 ppm groups were 28/64, 14/64, 25/62 and 48/64, respectively. For females the incidence was 5/64, 1/64, 2/64 and 8/64 in the control, 100, 500 and 2500 ppm groups, respectively. The combined incidence of liver tumors was statistically significant ($p < 0.001$) at the high dose level for males.

Male mice given CGA 64250 technical at 2500 ppm in the diet developed liver tumors. The **LOAEL** was 500 ppm (49.5 mg/kg/day) based on non-neoplastic liver effects (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)). The **NOAEL** was 100 ppm (10 mg/kg/day).

This oncogenicity study in the mouse is **acceptable/guideline** and satisfies the guideline requirement for an oncogenicity study (OPPTS 870.4200, §83-2b) in mice.

COMPLIANCE: This study predates the GLP guidelines.

Supplement to Document No. 004295, 005352 - DER for MRID No. 00129918, 00151502, 93194035. Oncogenicity Study in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Feeding - Rat; OPPTS 870.4300 [§83-5]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 tehnical(87.2-91.9% purity)

SYNONYMS: Propiconazole, Banner; Tilt; 1-[[2-(2',4'-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]-methyl]-lH-1,2,4-triazole

CITATION: Hunter, B; Slater, N; Heywood, R; Street, A; Prentice, D; Gibson,W; Gopinath, C. 1982. CGA-64250 Potential tumorigenic and toxic Effects in prolonged Administration to Rats. Huntingdon Research Centre, England, Report number CBG 193/8284: Test No.789023, Ciba-Geigy Ltd. Switzerland. September 30, 1982. MRID 00129918; CDL 00250787 through 00250790. Unpublished.

Ciba-Geigy Corp. (1985) Response to EPA Review of the Two-Year Dietary Oncogenicity and Chronic Toxicity Study with CGA-64250 Technical: Includes Historical Control Data and an Addendum to the HRC Report No. CBG 193/8284. MRID 00151502. Unpublished compilation. 373 p.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00129918 and Related MRIDS 00074494 and 00151502. Combined Chronic Oncogenicity/Toxicity Study in Rats. Study no. 193/8284. Prepared by Ciba-Geigy Ltd., July 3, 1990. MRID No. 93194035 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a 24-month oncogenicity study (MRIDs 00129918, 00151502 and 93194035), CGA 64250 technical (Batch No. P4-6; 87.2-91.9% purity) was administered to groups of Sprague Dawley CD rats (50/sex/dose) in the diet at concentrations of 0, 100, 500, or 2500 ppm (3.6, 18.1 and 96.4 mg/kg/day for males and 4.6, 23.3 and 100.6 mg/kg/day for females, respectively). A satellite group (30 rats/sex) was included at each concentration level. Of these, 10 rats/sex were used for hematological investigation, another 10/sex for blood chemistry and urinalysis investigations and the other 10/sex for interim sacrifice at one year and detailed microscopic examination with organ weight analysis. Diets were prepared weekly. During the first year of the study, the test material was ground directly into basal diet. During the second year, the test substance was dissolved in ethyl acetate prior to incorporation into the diet to improve the homogeneity of the test material in the diet (HED doc. No. 005352).

There were no compound-related clinical signs. Survival was not affected by the treatment. The total number of unscheduled deaths were 30, 31, 32, and 25 in males and 42, 36, 36 and 26 in females in the control, low, mid and high dose groups, respectively.

Food consumption was significantly lower ($p < 0.001$) for high dose females throughout the study and for high dose males from week 27 to termination ($p < 0.01$). Body weight gains of high dose male rats were significantly lower ($p < 0.001$; 84% of control during the first year, and 83% of control over the two year period). High dose female rats showed reduced body weight gain ($p < 0.001$; 65% of control during the first year and 66% of control during the entire two years, $p < 0.05$). These decreases in body weight gain were compound-related. Food conversion ratios were increased (poor utilization) in high dose males and females during the first 26 weeks. Water consumption of high dose female rats was lower than that of the controls during the study.

No toxicologically significant treatment-related effects were noted in hematology, blood chemistry and urinalysis parameters or in the ophthalmoscopy or hearing tests.

No macroscopic findings in rats sacrificed at 52 weeks were considered to be related to treatment. Liver weights were increased in high dose animals ($p < 0.001$; 122% and 144% of controls for males and females, respectively) at 52 weeks. Lipid

60

deposition in liver cells was also increased in high dose males (6/10 vs 2/10 in controls). Liver weights were also increased in high dose animals ($p < 0.001$; 125% and 121% of controls for males and females, respectively) at termination. Necropsy observations showed an increased incidence of grossly enlarged livers among high dose males which died during the study or were sacrificed at termination (18/45 vs 6/40 in controls for males and 19/45 vs 12/28 in controls for females at termination). Also, an increased incidence of discolored foci or puncta were found in the lungs of high dose females (17/45 vs 4/28 in controls at termination).

An increased incidence of foci of enlarged liver cells in high dose females was reported (13/67 vs 1/67 in controls) and it concluded that to be a treatment related effect.

Livers of high dose males showed increased vacuolated hepatocytes (44/65 vs 26/64 in controls) and ballooned cells (25/65 vs 15/64 in controls) which also exceeded historical control range suggesting a treatment-related effect.

A dose-related increase in liver cell lipid deposition in males was also apparent (4/64, 7/67, 15/66 and 17/65 in control, low, mid and high dose groups, respectively).

Additionally, the pancreas showed a dose-related effect in exocrine atrophy in female rats (1/60, 3/61, 6/62 and 9/65 in control, low, mid and high dose groups, respectively). The toxicological significance of this finding is considered questionable, however, since the incidence in the 2500 ppm group was comparable to the overall historical control value.

Luminal dilatation of the uterus also appeared to be a dose-related effect (4/58, 10/63, 9/63, 17/65 in control, low, mid and high dose groups, respectively). The incidence of this finding in the 2500 ppm group exceeded both the concurrent and overall historical control values and was considered treatment-related.

There were no treatment-related increase in the incidence of malignant tumors in treated rats.

The incidence of dermal fibroma was increased in the high dose males (5/61 vs 0/59 in the control). There was also an apparent increase in thyroid follicular adenocarcinoma (3/67) in high dose females vs 0/59 in controls. Additional data subsequently submitted by the registrant (Accession No. 07391829) in regard to these lesions revealed that because there was no dose-related trend in the incidences of dermal fibromas (8%) in males and

61

thyroid follicular cell adenocarcinomas in females (2/67; 3%) at 2500 ppm and the incidences were within their respective historical range, the occurrence of these was not considered to be treatment-related.

The **LOAEL** for CGA-64250 is 2500 ppm (96.4 mg/kg/day) based on liver lesions (vacuolation of hepatocytes in males, ballooned cells in the liver of males, foci of enlarged hepatocytes in females, and increased incidence of luminal dilation of the uterus) and reduced body weight gain in both males and females. The **NOAEL** is 500 ppm (18.1 mg/kg/day). The test material was not carcinogenic at the doses tested.

This chronic/oncogenicity study in the rat is **acceptable/guideline** and satisfies the guideline requirement for a chronic/carcinogenicity study (OPPTS 870.4300, 83-5) in rats.

COMPLIANCE: This study predates the GLP guidelines. A phase 3 summary (MRID 93194035) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

Supplement to Document No. 005352 - DER for MRID No. 00151515 Accession No. 00073928. Chronic Toxicity Study in Beagle Dogs. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Chronic Oral Toxicity (Dietary) - Dogs; OPPTS 870.4100 [§83-1b]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical, (90.2% purity)

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

CITATION: Johnson, WD, Thompson, SW and Becci, PJ. 1985. One-year subchronic oral toxicity study in beagle dogs with CGA-64250 technical. Food and Drug Resaearch Lab Study number 7737, Ciba-Geigy Corp, Greensboro, NC. May 28, 1985. MRID 00151515 & Accession No. 00073928. Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00151515. One-year Oral toxicity Study in the Dog: Propiconazole. Prepared by Ciba- Geigy Ltd., July 10, 1990. MRID No. 93194036. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 00151515), propiconazole was fed as CGA-64250 technical (90.2% purity, batch # FL-831527) to beagle dogs (7/sex/dose (control and high dose) and 5/sex/group (low and mid dose groups) at dietary dose levels of 0, 5, 50 or

250 ppm (time weighted average dietary concentrations based on mean food consumption are: 1.2±0.2, 13.0±2.0, 59.0±8.0 mg/kg/week or 0.2, 1.9, 8.4 mg/kg/day for males and 1.3±0.2, 13.0±2.0, 62.0±10.0 mg/kg/week or 0.2, 1.9 , 8.9 mg/kg/day for females, respectively) for a period of 52 weeks. These doses were based on a 3-month study in dogs fed 50, 250 or 1,250 ppm where a LOAEL of 250 ppm was set based on changes in the pyloric region of the stomach. All animals were sacrificed after 52 weeks except for two males and two females of the control and 250 ppm were sacrificed after a four week recovery period during of which these dogs were fed diets free of CGA-64250.

All dogs survived the 12 month treatment. No treatment related effects were noted in mean body weights, body weight gains, mean food consumption, hematologic and clinical chemistry, opthalmological findings, electrocardiograms, organ weights and gross pathological findings.

Histopathologic examinations revealed hypermia of the mucosa of the stomach in 3/5 of the 250 ppm males, and no comparable findings were seen in the control males. **Functional hypertrophy of the mammary gland** was reported in 1/5 control females, 2/5 receiving 50 ppm, and 3/5 receiving 250 ppm of the test material. All other findings including the necropsy and histopathological examination of the dogs in the recovery period were unremarkable.

Deficiencies in the study conduct included non homogeneous distribution of the test material in the mid-and high-dose groups during weeks 14-21. Analytical results showed the mean propiconazole concentrations for the 50 ppm diet ranged from 38 to 47 ppm and for the 250 ppm diet ranged from 161 to 518 ppm during this period. According to study authors this was due to mixing problems and crystallization of the test material during refrigeration storage. The test material was reported to be stable at room temperature, however, it was stored at room temperature only during the later half of the study and heated to 50-98° C prior to feed preparation. Nevertheless, the diet analysis data indicated the test material was stable throughout the study. The study is considered **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [870.4100, §83-1b] in dogs.

The **LOAEL** is 250 ppm (8.4 mg/kg/day), based on hypermia of the stomach in males (indicating mild irritation of the mucosa). The **NOAEL** is 50 ppm (1.9 mg/kg/day). However an OHEA and OPP work group (May 25, 1987) noted a mistake in the estimation of NOAEL dose and recommended instead the usual dose conversion factor for dogs of 1 ppm = 0.025. This revision results in slightly lower

NOAEL of 1.25 mg/kg/day. Accordingly the **LOAEL** is revised to 6.25 mg/kg/day.

COMPLIANCE: Signed and undated Quality Assurance statement was presented in the report. A phase 3 summary (MRID 93194036) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

ATTACHMENT

Chemical Name: Propiconazole Date: 5/25/88
CAS #: 60207-90-1

Office: ODW
Previously Verified: Yes, as 2 E-2 mg/kg/d
Previous Discussion Dates: 07/15/87

Outstanding Issues: None

1. Documentation: Adequate

2. Study: Appropriate

3. Uncertainty Factor: Appropriate

4. Modifying Factor: None

5. Calculation:

OHEA and OPP noted a mistake in the estimation of NOAEL dose (previous estimate 1.9 mg/kg/d) and recommended instead the usual dose conversion factor for dogs of 1 ppm = 0.025. This revision results in a slightly lower NOAEL of 1.25 mg/kg/d. The work group agreed.

6. Confidence Statement: Appropriate

7. Are the old issues resolved: None

8. New issues and additional work: None

9. New Status: RfD of 1.3 E-2 mg/kg/d

ON IRIS:		NOT ON IRIS:	
_____	No change to IRIS	___X___	(IR)Verified (V)
_____	Pending change to IRIS (RE)	_____	Under Review (UR)
_____	Withdrew and Replace (WV)	_____	Not verified (NV)
_____	Withdrew & Still Under Review (WR)		

New Verification Date: ___5-25-88___

Supplement to HED Document No. 005782 & 010242 - DER for MRID No. 42415701, 00164469; and MRID 45345901: CGA 64250 Technical - Dermal Absorption in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan, Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Dermal Absorption - Rat; OPPTS 870.7600 [§85-3]

DP BARCODE: D272339 SUBMISSION CODE:S591835, S594147
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250, Propiconazole

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

CITATION: Murphy T. 1986. Dermal Absorption of ^{14}C-Propiconazole: Addendum to ABR-86053. Study number 86064, Ciba-Geigy Corp, Greensboro, NC. September 30, 1986. MRID 42415701. Unpublished.

Murphy, T.; Brown, K.; Doornheim, D.; *et al*. 1986 Dermal Absorption of Carbon 14-Propiconazole in Rats after a Ten-Hour Exposure Period: Report No. ABR-86053. Unpublished study prepared by Ciba-Geigy Corp. 76 p., MRID 00164469

Murphy, T. 2001. Dermal Absorption of ^{14}C-Propiconazole: Addendum to ABR-86053, MRID 42415701. Study number 1596-01, Syngenta Crop Protection, Inc., Greensboro, NC. March 2, 2001. MRID 45345901. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY: In a dermal absorption study (MRID's 42415701, 45345901), groups (4/group) of young adult male, Harlan Sprague-Dawley rats (age not given) were exposed to triazole-[3,5-]^{14}C-

CGA-64250 (95% radiochemical purity, specific activity 28.2 µCi/mg for low and mid-dose levels and 2.01 µCi/mg for the high-dose level) at doses of 0.1, 1.0 or 10 mg/rat (0.01, 0.1 or 1 mg/cm^2, respectively) to a 10 cm^2 shaven dorso-lumbar area. 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. One group of four rats/dose were exposed for 24 hours, while two other groups of four rats each/dose were exposed for 10 or 24 hours followed by a 72-hour depletion phase. This study is an addendum to an earlier study where groups of four male rats each were treated similarly but exposed for 2, 4 or 10 hours (MRID 00164469). In both studies, following the exposure period, the test compound remaining on the skin was removed with a soap rinse. Fecal and urinary samples were collected at the end of the exposure periods and at 24 hour intervals (for the depletion groups) following the exposure.

At sacrifice time rats were anesthetized and blood colleted. 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 % for MRID 42415701 and 86.6 to 112.6% for MRID 00164469.

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 µg/cm^2 (57.13, 27.14 and 30.10% of total dose 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. The results of the earlier study (MRID 00164469) demonstrated that 26-35% of the applied radioactivity (at all dose levels) is absorbed within the first two hours and remained fairly constant for the longer exposure periods of 4 and 8 hours except for the low dose of 0.01 mg/cm^2 where it increased to 54%. The average dermal absorption of propiconazole over a 10 hour period at an exposure level of 0.01 mg/cm^2 is approximately 40%. The attached appendix provides a summary of both studies.

The two studies were classified **Acceptable/guideline** and both satisfy the guideline requirement (870.7600; 85-3) for a dermal absorption study.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided for MRID 00164469 and 42415701.

APPENDIX

SUMMARY TABLE OF DERMAL ABSORPTION OF ^{14}C-PROPICONAZOLE IN RATS

Fraction	Percent of the applied dose at the application rates of[4]		
	0.01 mg/cm^2	0.1 mg/cm^2	1.0 mg/cm^2
24-hr exposure*			
Absorbed[1]	47.44	10.22	8.46***
Absorbed including skin[2]	57.13	27.14	39.47***
Unabsorbed[3]	48.17	55.70	57.11***
10-hr exposure + 72 hr depuration*			
Absorbed[1]	42.37	21.46	30.97
Absorbed including skin[2]	48.25	25.16	37.02
Unabsorbed[3]	59.79	61.49	58.37
24-hr exposure + 72 hr depuration*			
Absorbed[1]	54.71	29.83	29.83
Absorbed including skin[2]	59.41	35.36	42.39
Unabsorbed[3]	42.33	59.92	48.49
2-hr exposure**			
Absorbed[1]	14.68	2.70	1.42
Absorbed including skin[2]	34.74	26.15	30.10
Unabsorbed[3]	77.87	79.07	72.88
4-hr exposure**			
Absorbed[1]	12.79	20.65	1.34
Absorbed including skin[2]	36.73	36.12	31.07
Unabsorbed[3]	58.02	69.22	64.76
10-hr exposure**			
Absorbed[1]	39.67	11.20	4.81
Absorbed including skin[2]	53.70	36.19	29.29
Unabsorbed[3]	43.63	62.51	57.32

* Data extracted from Tables I, II and III of MRID 42415701
** Data extracted from Tables I, II AND III of MRID 00164469
*** Data extracted from Appendix Table VII of MRID 45345901
[1] Sum of urine, feces, blood and carcass
[2] Sum of urine, feces, blood, carcass and skin
[3] Sum of soap rinse, water rinse, bridge rinse, paper, paper rinse, bandage rinse, gauze squares, and cage wash
[4] Mean of four rats per time point

69

Supplement to hed Document No. 005782 - DER for MRID No. 00164795:Propiconazole: Metabolism in the Mouse and Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasa, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Metabolism-Mouse & Rat OPPTS 870.7485 [§85-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250, Propiconazole; radiochemical purity 97%

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

CITATION: Bissig, R. 1986. The Metabolism of (U-^{14}C)-Phenyl CGA-64250 in Mice After Preatrment with Unlabelled CGA 64250. Study No. 6/86, MRID 00164795 (Accession No. 265794) May 20, 1986. Unpublished.

SPONSOR: Ciba Geigy Corporation, North Carolina

EXECUTIVE SUMMARY: In a metabolism study [MRID 00164795], the absorption, distribution, metabolism and excretion of (U-^{14}C)-phenyl labeled propiconazole was investigated in CD-1 mice and Tif:RAI F (SPF) rats. Male and female mice (5/dose level) were fed ad libitum unlabeled CGA 64250 (Batch No. OP 412127, 91.1% purity) in the diet for 21 days at levels of 5, 100 or 2500 ppm followed by a single oral dose of the radiolabeled CGA 64250 (Batch No. GAN-VA-43) at the corresponding levels (equivalent to 0.81, 16.8 and 434 mg/kg for males and 1.02, 21.5 and 475 mg/kg for the females). Three female mice were given a bolus dose of 600 mg/kg ^{14}C-CGA 64250 without pretreatment of unlabeled compound (these mice showed severe signs of toxicity and two died 48-72 hours post dosing). Two male rats were given 9.4 mg/kg single oral dose of the ^{14}C-CGA 64250 without pretreatment of unlabeled compound. After ^{14}C-CGA 64250 dosing, animals were

kept in glass metabolism cages. Urine and feces were collected at 24 hour intervals. Animals were killed 4 days post ^{14}C dosing. Blood, liver, kidneys, lungs and remaining carcass were taken for analysis.

Excretion

Mice pre-treated with the unlabeled CGA 64250 excreted 83-103% of the administered ^{14}C radioactivity within 96 hours (mostly within the first 24-48 hours) in the urine and feces. More radioactivity (particularly at the higher doses of 100 and 2500 ppm) was excreted in the urine than in the feces (1.5-3.7x) in males and females. The high dose females excreted the least amount (83% of the administered dose (AD). Total recovered radioactivity ranged from 88-106% of the AD. The male rats excreted nearly equal amounts of the radioactivity in urine (48%) and feces (54%).

Tissue Disribution

Tissues and carcass residues were less than 0.55% of the AD in treated rats and mice. Four days post dosing with ^{14}C-CGA 64250, residues were detected in the liver in rats and liver, kidneys and carcass in mice.

Urinary Metabolites

Two dimensional TLC revealed 15-30 metabolites in the 0-24 urine samples (identified in the report by their TLC code). Metabolites U_1, U_2, U_9, U_{12}, U_{17}, U_{18} representing 5-19%, 6-73%, 2-8%, 2-22%, 2-3% and 1-16% of the urine radioactivity, respectively were the most predominant in the two species. Metabolite U_2 was highest in the male mice urine (61-73%). Female mice urine contained 29-36% while the male rat had the least (6%) of the U_2 metabolite. The U_{12} fraction was another example of species and sex difference in metabolic products. At 5 and 100 ppm female mice (and the male rats) excreted more of the U_{12} metabolite than in the other groups (18 and 21% in female mice, respectively and 22% in male rats). In an earlier study this metabolite was identified as α-hydroxy-carboxyacid (metabolite CU).

When mouse urine was incubated with β-glucuronidase then 75-85% of the U_2 fraction disappears giving rise to a more unpolar U_{18} fraction. In rat urine, however, the most polar fraction U_1 completely disappears after β-glucuronidase incubation and forms several unpolar fractions while the U_2 fraction of the rat urine

71

is not significantly affected. The U_{18} fraction consisted of at least two compounds, one is the alcohol CGA 91305 and the other is the analogus ketone CGA 91304. The major urinary metabolite isolated from the U_2 fraction was determined to be Met IU, the glucuronic acid conjugate of metabolite CGA 91305.

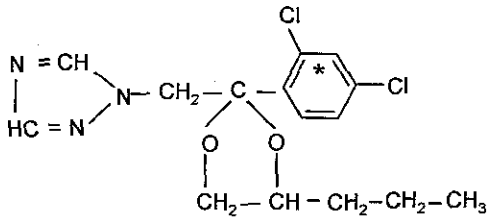
Metabolic Pathway

It was concluded that the major metabolic pathway in mice proceeds via elimination of the dioxolane ring leading via ketone formation (CGA 91304) to the corresponding acid to yield metabolite CGA 91305. In males this represents 30% of the AD whereas in the females it represents 15% of the AD. In rats, the non-polar metabolite fractions U_{15} through U_{18} represent metabolites where the dioxolane ring has been cleaved. In conclusion mice cleared the dioxolane ring to a greater extent (70 & and 40% for males and females, respectively) than do male rats (30%).

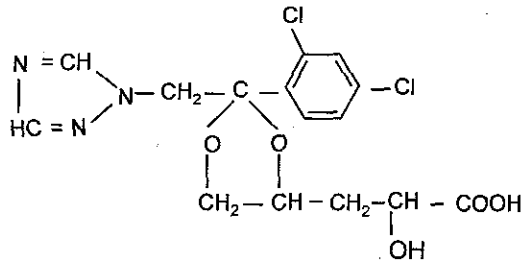
This part of the metabolism study in the mouse investigating the absorption, distribution, metabolism and excretion of propiconazole following single oral dose or repeated oral doses is classified **Acceptable/non-guideline.** It presents the comparative differences in the metabolism of CGA 64250 in mice and rats.

COMPLIANCE: Signed and dated, Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided.

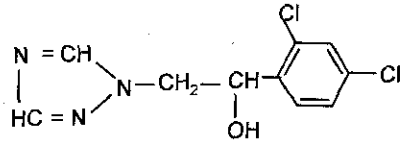
APPENDIX: REFERENCE COMPOUNDS



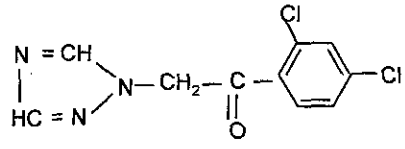
CGA 64250



Met. Cu



CGA 91305



CGA 91304

73

Supplement to Document No. 010014 and 011313 - DER for MRID No. 42403901:Propiconazole: Metabolism in the Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Metabolism-Rat
OPPTS 870.7485 [§85-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250, Propiconazole; radiochemical purity >98%

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

CITATION: Mucke, W. 1983. The Metabolism of CGA-64250 in the Rat. Study number PR 24/83. Dept. of R& D Plant Protection, Ciba Geigy Corporation, Switzerland (Novartis). MRID 42403901. September 1, 1983. Unpublished.

SPONSOR: Ciba Geigy Corporation, Switzerland

EXECUTIVE SUMMARY: In a metabolism study [MRID 42403901], the metabolism and excretion of propiconazole labeled with ^{14}C at the triazole-[3,5] position was investigated in TIF: RIA f (SPF) male rats (number and age of animals not given) orally gavaged a single dose of 31.4 mg/kg, dissolved in water/ethanol/propylene glycol 200 (50/30/20 v/v/v). Animals were house individually in metabolism cages.

This study focused on the identification of the urinary and fecal metabolites. Several analytical techniques were used to separate the various metabolites including high performance liquid chromatography, thin layer chromatography, methylation,

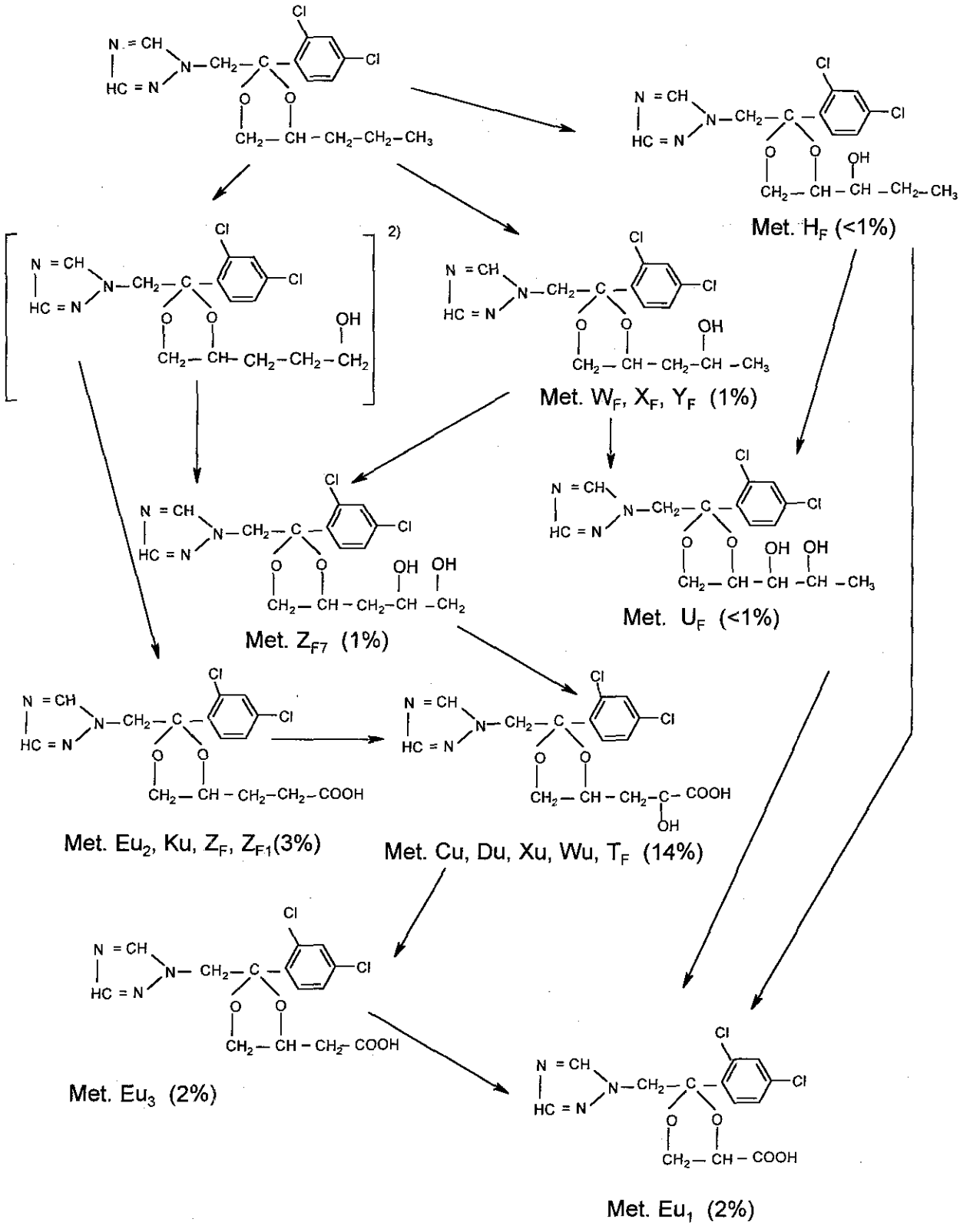
acetylation, sylation and other derivitization techniques.

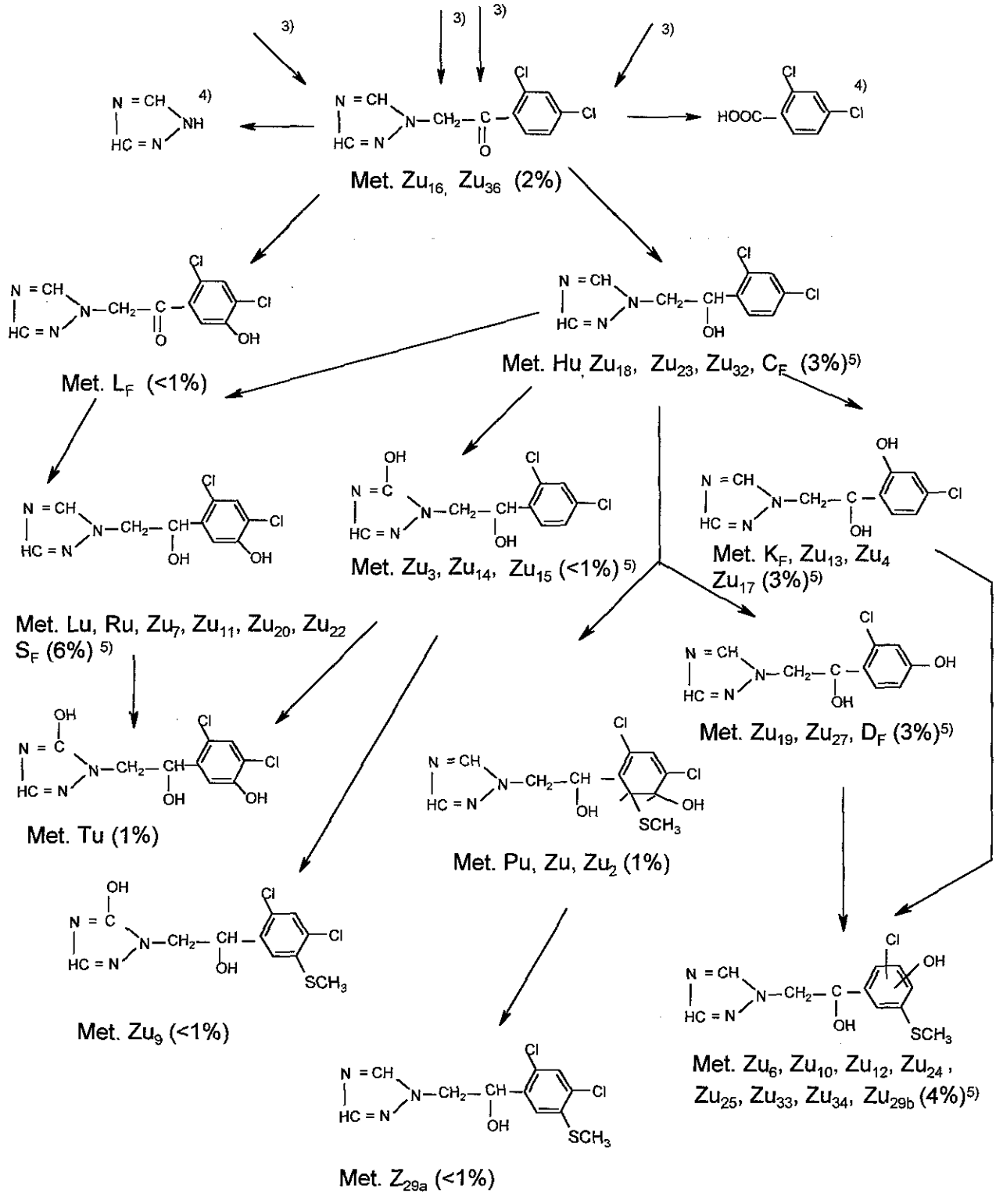
The test compound was rapidly metabolized with 81, 94 and 96% of the radioactivity appearing in the urine and feces 1,2, and 3 days, respectively after dosing. The ratio of the urine to feces radioactivity was approximately 5:4. The parent compound is extensively metabolized; only a small percentage remained unabsorbed and appeared in the feces. The n-propyl side chain is first metabolized to α-, β- and γ-hydroxy derivatives and then to α,β- and β,γ- diols. The α, β- diol is further metabolized to α-hydroxy carboxylic derivative, a major metabolite (metabolite U8, 11%) appearing in the urine. The side chain is sequentially decarboxylated to yield acetic and formic acid derivatives. Once the dioxolane derivative ring is cleaved, a wide variety of metabolic reactions occurs, leading, in general, to the hydroxylation of the dichlorophenyl and triazole rings. Sulfation appeared to be the preferential route of secondary metabolism and accounted for 5.5% of the dose. A proposed metabolic pathway in the rat is found in appendix A.

This study classified **Acceptable/guideline**. It partially satisfies the guideline requirement for a metabolism study (870.7485, §85-1) because absorption and tissue distribution of radioactivity were not determined in this study.

COMPLIANCE: Signed and dated GLP, Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided.

Appendix 1: Proposed Metabolic Pathway of ^{14}C-Triazole Propiconazole in the Rat (taken from of study MRID 42403901 (Fig 16): values represent percent of dose) [1)]





1) These figures are based on the amounts of metabolites actually isolated
2) Hypothetical intermediate
3) Metabolite Zu_{16} might be metabolically formed from all metabolites above
4) Artifacts
5) Metabolites partially excreted as sulfatic and/or glucuronic acid conjugate

Supplement to HED Document No. 008052 - DER for MRID No. 41326701:Propiconazole: Metabolisn in the Rat. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Metabolism-Rat
OPPTS 870.7485 [§85-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250, Propiconazole; radiochemical purity >99%

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

CITATION: Creswell, D.G. 1989. (U-^{14}C)-Phenyl CGA-64250: Absorption, Distribution, Metabolism and Excretion in the Rat. Study number Hazelton UK # 380/105, MRID 41326701. June 2, 1989. Unpublished.

SPONSOR: Ciba Geigy Corporation, North Carolina

EXECUTIVE SUMMARY: In a metabolism study [MRID 41326701], the absorption, distribution, metabolism and excretion of propiconazole labeled with (U-^{14}C)-Phenyl was investigated in groups of (5/sex/group) Sprague-Dawley rats (Crl:CD(SD)BR strain) following oral or intravenous (iv) administration at dose levels of 0.5 mg/kg. Additionally, one group was administered daily single oral dose of 0.5 mg/kg of the non-radiolabeled compound for 14 days followed with a single oral dose of 0.5 mg/kg of the radiolabeled material 24 hours after the last dose. Another group was administered a single oral dose of 50 mg/kg of the radiolabeled compound. Animals were housed individually in metabolism cages. Urine and feces were collected at regular intervals and analyzed by two dimensional thin layer chromatography and autoradiography. Tissues were collected at sacrifice time (168 hours) and radio-assayed.

Administration of 0.5 mg/kg of radiolabeled CGA 64250 to rats by oral or iv routes resulted in similar patterns of elimination, possibly as a result of biliary excretion. Renal elimination data suggest that 35-50% of the oral dose was absorbed. More than 90% of the administered radioactivity was eliminated in the urine and feces (including cage washes) after 168 hours of dosing. Most of the excreted radioactivity occurred within the first 48 hours of treatment. Traces or non detectable levels were seen in the tissues and expired air. Female rats appeared to eliminate more of the radioactivity in the urine than in the feces(46.3% vs 39.0% in the orally dosed; 43.8% vs 37.0% in the iv dosed). While male rats eliminated more radioactivity in the urine than in the feces in most of the groups except for the iv group where urine and fecal elimination were about equal. **No significant differences in the excretion pattern were seen between the low and high oral dose groups or the repeated dosing group. The distribution of radioactivity in tissues was similar in low and high dose groups.**

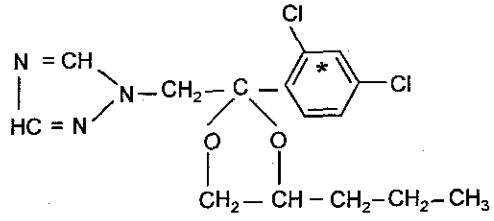
Examination of the pooled urine and fecal samples indicated that (U-^{14}C)-Phenyl labeled CGA 64250 was extensively metabolized into 24 and 47 different radiolabeled components, respectively. The latter may reflect a difference in assay sensitivity as well as a dose level effect. **Within each sample type, the pattern of metabolites varied according to sex and dose group.** The radiolabled parent compound was only detected in the urine of the iv group males and females (27.1 and 29.9% of the urine radioactivity in males and females, respectively). In the iv urine radiolableled material co-chromatographing with standards CGA 188245 (61.8% in males, 2.4% in females), CGA 217495 (8.9% in males, 58.3% in females), CGA 91304 (2.3% in males only), CGA 118244 (3.6% in females only). These metabolites were also detected to varying degrees in the urine of the orally dosed groups. In the feces, no parent material was detected in the iv group, but detected in the other groups (6.8-17.6% of the fecal radioactivity in males and females). Radiolabeld materials co-chromatographing with standards CGA 91305, CGA 188245 and CGA 177291 were reported ranging from 0.5% - 10.9% of the fecal radioactivity in males and females or in one sex alone. Most of the fecal radioactivity was not characterized.

(U-^{14}C)-Phenyl radiolabeled is extensively metabolized in male and female rats following oral or iv administration. The proposed metabolic pathway involves initial side chain oxidation giving the hydroxylated propyl derivative or replacement of the propyl group by carboxylic acid. The alkyl side chain attached to the dioxolane ring in CGA 64250 is probably attacked with the possible loss of the dioxolane ring itself.

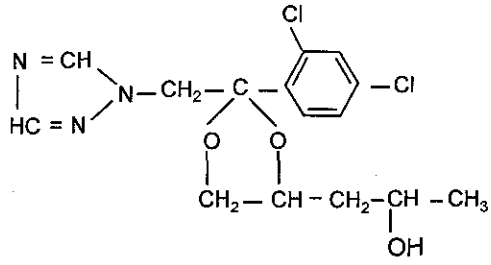
This study is classified **Acceptable/guideline.** However, it partially satisfies the guideline requirement for a metabolism study (85-1) because most of the metabolites were not identified.

COMPLIANCE: Signed and dated GLP, Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided.

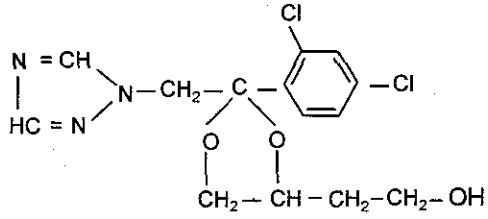
APPENDIX: REFERENCE COMPOUNDS



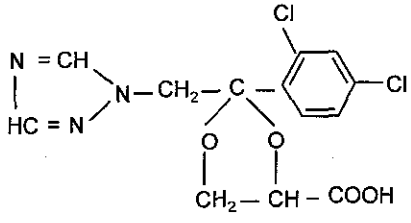
CGA 64250



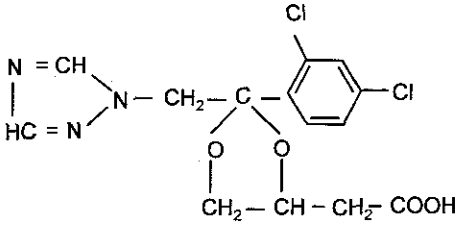
CGA 118244



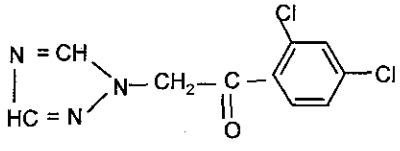
CGA 118245



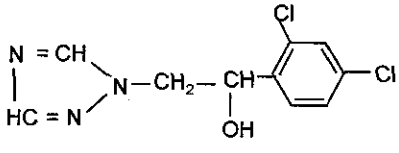
CGA 217495



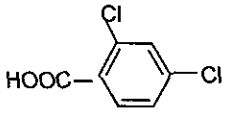
CGA 217496



CGA 91304



CGA 91305



CGA 177291

Supplement to HED Document No. 005782 - DER for MRID No. 00074506 & 00074507: Propiconazole: Metabolism in the Mouse. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan, Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Metabolism-Rat OPPTS 870.7485 [§85-1]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE: 122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250, Propiconazole; radiochemical purity >98%

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

CITATION: Muecke, M. 1979. Characterization of Urinary and Fecal Metabolites of Rats after Oral Application of CGA 64250. Study No. 35/79, MRID 00074506 (Accession No. 265794) August 31, 1979. Unpublished.

Muecke, M. 1981. The major Metabolic Pathways of CGA 64250 in the Rat. Study No. 9/81, MRID 00074507 (Accession No. 265794) March 13, 1981. Unpublished.

SPONSOR: Ciba Geigy Corporation, North Carolina

EXECUTIVE SUMMARY: In a metabolism study [MRID 00074506 & 00074507], urinary and fecal metabolites of (U-^{14}C)-phenyl or ^{14}C-triazole ring labeled propiconazole administered to Tif:RAI F (SPF) male rats were investigated. The triazole-[3,5-^{14}C] CGA 64250 (specific activity 23.1 uCi/mg) was given to 20 male rats at an average single oral dose of 31.4 mg/kg. The phenyl-[U-^{14}C] CGA 64250 (specific activity 38.9 uCi/mg) was given to 3 male rats at an average single oral dose of 32.5 mg/kg. Animals were kept in individual metabolism cages. Urine and feces were collected and pooled for an unspecified period of time and analyzed for radioactivity.

The study mainly focused on the analysis of urinary and fecal metabolites. Within 3 days >95% of the administered triazole labeled dose was excreted in urine (52%) and feces (43%). Animals treated with the phenyl label showed a similar pattern of excretion in urine (51%) and feces (48%).

Examination of the 0-24 hour urine by two dimensional TLC revealed 12 metabolites in both the triazole and phenyl labeled and a 13th metabolite in the triazole labeled compound. No parent material was detected. When the urine was incubated with β-glucurodinase or with β-glucurodinase/aryl sulfatase certain metabolite fractions disappeared suggesting the presence of glucuronic acid and sulfuric acid conjugates. Two other fractions co-chromatographed with CGA 77502 and CGA 58533. High voltage electrophoresis showed 80% of the urinary metabolites to be acidic and fecal metabolites were some what polar.

The percentages of fecal metabolites extracted and distributed at various pH's were not substantially different between the triazole and phenyl labeled CGA 64250. TLC of the fecal extracts revealed at least 8 metabolites, which were less polar than the urinary metabolites. TLC also indicated the presence of metabolites CGA 77502 and CGA 58533 in addition to unchanged parent material (5% of fecal radioactivity).

The similarities in the excretion pattern and metabolite distribution from the two different lables suggest that the bridge between the phenyl ring and the triazole ring remained intact.

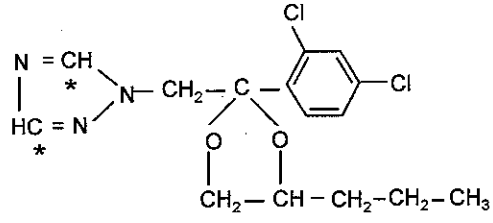
The proposed major metabolic pathway appears to involve the cleavage of the dioxalone ring with subsequent dechlorination and conjugation and through the oxidation of the propyl side chain. The metabolic profile of both urine and feces appear to be similar except for the presence of parent material in the feces while the urine had conjugated phenolic metabolites.

This part of the metabolism study in the rat investigating the urinary and fecal metabolites of propiconazole labeled in two different positions following single oral dose is classified **Acceptable**. However, it partially satisfies the guideline requirement for a metabolism study (870.7485, §85-1) because it did not provide absorption and pharmacokinetic data.

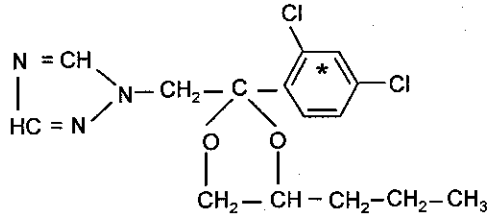
COMPLIANCE: Signed and dated, Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided.

83

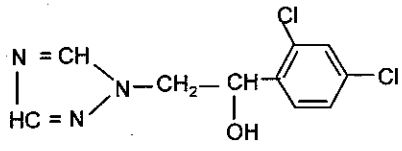
APPENDIX 1: REFERENCE COMPOUNDS



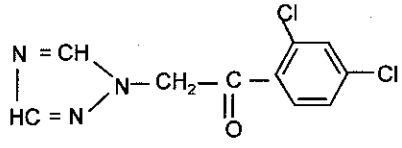
CGA 64250, triazole label



CGA 64250, phenyl label



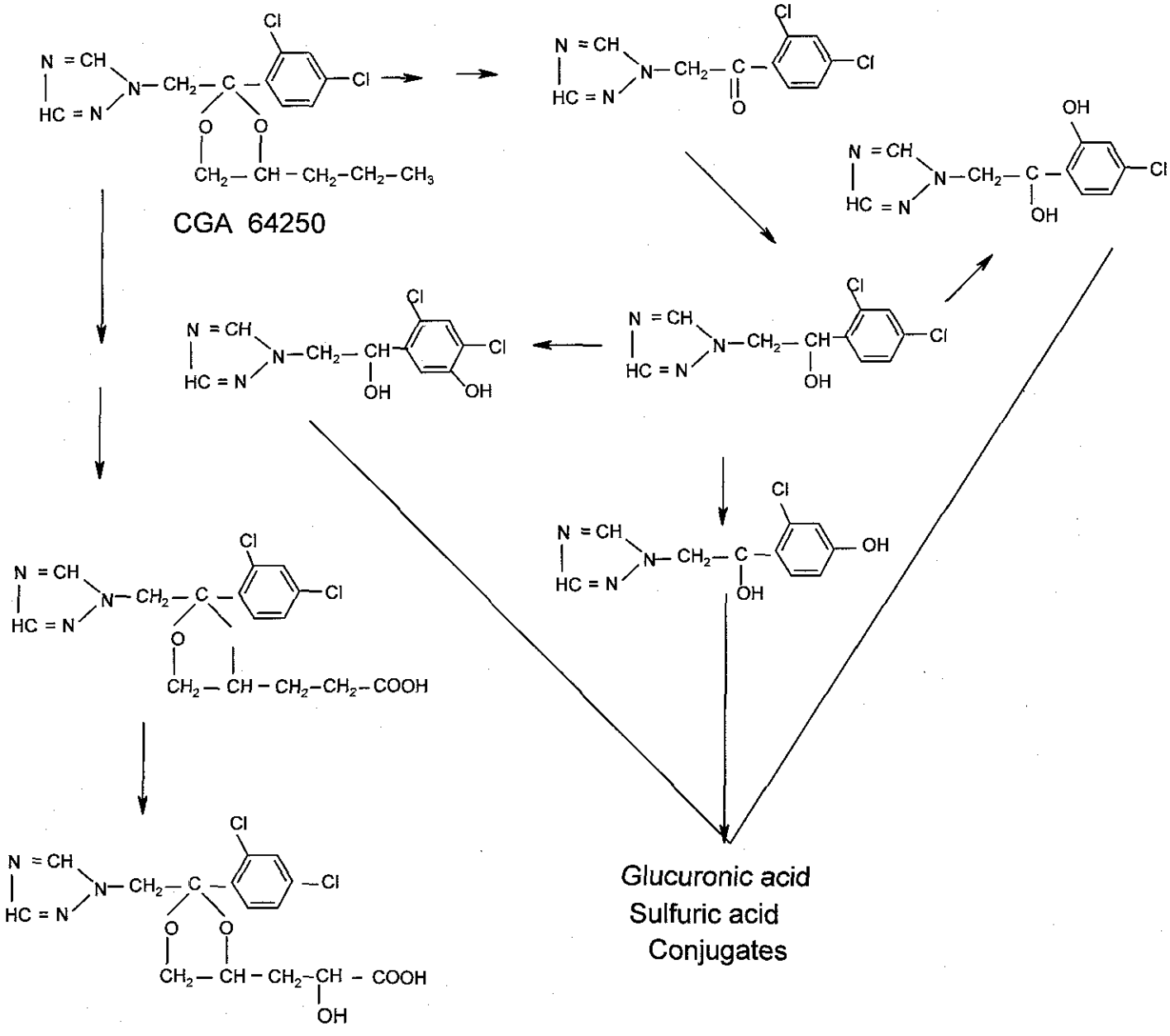
CGA 77502



CGA 58533

84

Appendix 2: Proposed major metabolic pathways of CGA 64250* in the Rat



* Chart from page 11 of MRID 00074507: ^{14}C-triazole or phenyl labeled propiconazole

85

Supplement to Document No. 006731 - DER for MRID No. 40425001: CGA 64250 Technical - Teratology Study in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rat; OPPTS 870.3700 [§83-3a]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (91.7-92.3%)

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

CITATION: Marcsisin, JF, Wimbert KV, Giknis, MLA, Arthur AT, and Yau AT. 1987 .CGA 64250 Technical - Teratology (Segment II) Study in Rats. Study number Toxicology/Pathology Report 86004 (MIN 852 148), Pharmaceutical Division, Ciba-Geigy Corp. January 28, 1987. MRID 40425001. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 40425001), CGA 64250 technical(92.1% purity, Batch no. FL 850083) was administered to 24 CL:COBS CD (SD) BR VAF/PLUS virgin female rats/dose by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 30, 90 or 300 mg/kg/day from days 6 through 16 of gestation. High dose animals initially received 360 mg/kg/day up to five days, but because of severe symptoms it was reduced to 300 mg/kg/day.

Severe compound-related maternal toxicity was observed at the

high dose level during the first five days of dosing beginning on day 8 of gestation at 360 mg/kg/day. These included statistically significant increases in the incidence of lethargy, ataxia, salivation, and biologically significant increases in rales, prostration, hypothermia and bradypnea. The incidence of these effects versus control is as follows: lethargy (9/23 vs 0/24 in controls), salivation (4/23 vs 0/24 in controls) and ataxia (3/23 vs 0/24 in controls). After lowering the dose to 300 mg/kg/day on day 6, the severity and frequency of these effects decreased rapidly. At the lower doses with the exception of one animal of the 90 mg/kg/day group exhibiting rales, there were no treatment related clinical observations. In another separate study (MRID 40425002) imazalil was administered to a large number of pregnant females during gestation day 6-17 at 0 (178 females) or 300 mg/kg/day (179 females). In this study severe clinical toxicity (ataxia, coma, lethargy, prostation, labored respiration and salivation) was reported in treated animals.

Mean food consumption was significantly reduced ($p<0.05$) in the 300 mg/kg/day group on days 7-8, 8-9 and 9-10 and in the 90 mg/kg/day group on days 8-9 and 10-11. Maternal body weights were not affected by the treatments. Maternal body weight gains were significantly decreased ($p<0.05$) in the 90 mg/kg/day group (44% of controls) and in the high dose group (38% of controls) during gestation days 6-8 only. No significant treatment-related effects on uterine weights, corpora lutea, live and dead fetuses, fetal weights, and resorption were reported.

Based on the combined findings of this study and study MRID 49425002, the maternal toxicity **LOAEL** of Propiconazole is 300 mg/kg/day, based on severe clinical toxicity (ataxia, coma, lethargy, prostation, labored respiration and salivation). The maternal toxicity **NOAEL** is 90 mg/kg/day.

Fetotoxic effects observed included a high incidence of rudimentary ribs, though not statistically significant but part of dose related trend (0.7%, 3% and 39% in the 30, 90 and 300 mg/kg/day groups, respectively vs 0% in the controls), a high incidence of unossified sternebrae (57%, $p \leq 0.05$ in the 90 mg group, and 72%, $p \leq 0.01$ in the 300 mg group vs 38% in the controls), as well as increased incidence of shortened renal papillae(26% in the 90 mg group (not statistically significant) and 39% in the 300 mg group, $p \leq 0.01$ vs 23% in the controls) and absent renal papillae (5% in the 90 mg group (not statistically significant) and 11% in the 300 mg group, $p \leq 0.01$ vs 3% in the controls) and dilated ureter (43% in the 300 mg

87

group, $p \leq 0.01$ vs 27% in the controls). External and visceral examination revealed a very low incidence of cleft plate malformations in the 90 mg group (0.3%) and in the 300 mg group (0.7%) and considered to be "probably compound related". Historical controls in 19 teratology studies from this laboratory had no incidence of cleft palate. The cleft palate incidence in the current study was probably under reported because only half of the fetuses were examined viscerally. It was also concluded that the low incidence of this finding along with skeletal anomalies was indicative of delayed development. The cleft palate finding at 300 mg/kg/day was also confirmed in the MRID 40425002 study.

The developmental toxicity **LOAEL** of Propiconazole is 90 mg/kg/day, based on increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae. The developmental toxicity **NOAEL** is 30 mg/kg/day.

This developmental toxicity study in the rat is classified as **acceptable** and **satisfies** the guideline requirement for a developmental toxicity study [870.3700] in rats.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

Supplement to Document No. 006731 - DER for MRID No. 40425002: CGA 64250 Technical - Teratology Study in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rat; OPPTS 870.3700 [§83-3a]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (91.7-92.3%)

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

CITATION: Mallows, S, Levy E, Giknis, MLA, and Yau AT. 1987. A Modified Teratology Study in Albino Rats with CGA-64250. Study number Toxicology /Pathology Report 86189 (MIN 862244), Pharmaceutical Division, Ciba-Geigy Corp. January 16, 1987. MRID 40425002. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a non guideline developmental toxicity study (MRID 40425002), CGA 64250 technical(92.1% purity, Batch No. FL 850083) was administered to CL:COBS CD (SD) BR VAF/PLUS virgin female rats by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0 or 300 mg/kg/day from days 6 through 15 of gestation. The control group comprised 178 sperm positive animals and the compound treated group comprised 189 sperm positive animals. The study was intended to confirm the finding of cleft palate in the previous study (MRID 40425001).

The death of two dams from the treated group was considered incidental. Severe maternal toxicity was observed during the treatment period beginning on gestation day 6 (see attached table) and included a statistically significant increase in the incidence of ataxia (42% vs 0 in controls), coma (9% vs 0 in controls), lethargy (44% vs 0 in controls) , prostration (3% vs 0 in controls), audible respiration (4% vs 0 in controls), labored respiration (11% vs 0 in controls), and salivation (20% vs 0 in controls) in addition to a biologically significant incidence of ptosis (0.5% vs 0 in controls), lacrimation (2% vs 0 in controls), pale color (2% vs 0 in controls) and death (1% vs 0 in controls).

Mean food consumption was significantly lower (60-92% of the control values, $p<0.05$) in the treated group during the dosing period. Body weight gains were significantly lower (68% of controls, $p<0.05$) in dosed animals during GD 6-16.

There were no significant differences between dosed and control animals with respect to fetal sex ratio or mean number of corpora lutea, implantation sites and dead fetuses. The mean number of live fetuses was significantly (95% of controls, $p<0.05$) lower in dosed animals, due to lower mean implantation sites, and higher mean total resorption in the dosed animals, although not significantly different from controls. Mean fetal weights for both males and females (95% of controls, $p<0.001$) were significantly lower in dosed animals.

Fetuses were examined for external abnormalities only and there were no statistically treatment related , external, gross observations among fetuses. Cleft palate was reported in 2/2064 fetuses of dosed animals and 0/2122 of control fetuses. The incidence of cleft palate in controls for all teratology studies (not including this one) conducted at this laboratory during 1983-1985 was 0/5431. This study confirms the findings of cleft palate in the previous guideline study (MRID 40425001).

This study is **acceptable/non-guideline** study and provides supplementary information to a previously acceptable guideline study (MRID 40425001) for a developmental toxicity study [870.3700 (83-3)] in rats.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

TABLE 6.1 OF Study Report MRID 40425002 PG0025 OF 0408

CGA 64250
MIN 862244
Rat Teratology

TABLE 6.1.
Incidence of Clinical Observations [1]

Observation	Treatments (mg/kg/day)	
	0	300
Alopecia	18/178	14/189
Ataxia	0/178	79/189**
Blood/crust around mouth	1/178	1/189
Blood around vagina	0/178	1/189
Chromodacryorrhea	0/178	1/189
Comatose	0/178	17/199**
Death	0/178	2/189[a]
Hypothermia	0/178	1/189
Lacrimation	0/178	4/189
Lame/disused/swollen limb	0/178	1/189
Lean	0/178	1/189
Lethargic	0/178	83/189**
Mass-right axillary region	0/179	1/189
Opacity - left eye	0/178	1/189
Pale in color	0/178	3/189
Prostrate	0/178	5/189*
Ptosis	0/178	1/189
Respiration audible	0/178	7/189**
Respiration labored	0/179	20/189**
Salivation	0/178	37/189**
Soft stool	0/178	1/189
Sore/scab	1/178	1/189
Unthrifty	0/178	1/189
Water deprived	0/178	2/189

*Different from the control group at $p \leq 0.05$.
**Different from the control group at $p \leq 0.01$.
[1] The incidence reported is based on the number of animals displaying the clinical sign on at least one occasion after the initiation of treatment.

[a] One dam (#1222) died on day 12 of presumed gestation due to a dosing accident and one dam (#1319) was sacrificed on day 17 of gestation due to early delivery, therefore there were a total of 4 deaths in this study but only two were treatment-related and are included on this table.

J6/36 (MIN 862244)

91

Supplement to HED No. 005782 - MRID 00164800 (Accession No.00265796) and HED No. 006731 - DER for MRID No. 40425004: CGA 64250 Technical - Teratology Study in Rabbits. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rabbit; OPPTS 870.3700 [§83-3b]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (92.1%)

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

CITATION: Raab, DM; Yourneff, MA; Giknis, MLA; and Yau, AT. 1986. CGA-64250 Technical - A Teratology Study in New Zealand White Rabbits. Study number Toxicology /Pathology Report 86043 (MIN 852172). Pharmaceutical Division, Ciba-Geigy Corp. MRID 00164800 August 1, 1986. Unpublished.

Raab, DM; Yourneff, MA; Giknis, MLA; and Yau, AT. 1987. CGA-64250 Technical - A Teratology Study in New Zealand White Rabbits. Study No. Toxicology /Pathology Report 86043 (MIN265796) Supplement to Accession No. 265796. Pharmaceutical Division, Ciba-Geigy Corp. June 16, 1987. MRID 40425004. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 00164800), CGA 64250 technical(Batch No. FL850083, 92.1% purity) was administered to groups (19/group) of artificially inseminated New Zealand white

rabbits by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 100, 250 or 400 mg/kg/day from days 7 through 19 of gestation.

One animal from each of the mid-dose groups was found dead. In high-dose animals, 5/19 does were sacrificed early due to abortion or early delivery (statistically significant, $p<0.05$ compared to control 1/19). In the mid dose(250 mg/kg/day) group, one doe aborted early. One control animal delivered early.

Among animals of the high dose group, an increased incidence of stool alterations (decreased/no/soft; 18/19 vs 11/19 in controls, $p<0.05$) was observed, possibly compound related.

During the dosing period (days 7-19), the high and mid dose animals had a significant ($p<0.05$) decrease in food intake (43 - 63% of the controls and 58-78% of the controls in the high- and mid-dose groups, respectively) and a severe decrease in the maternal body weight gain, but rebounded to normal after withdrawal of the test compound. During GD 7-10, the maternal animals had a weight loss of 0.047 and 0.111 kg at 250 and 400 mg/kg, respectively, compared to a weight gain of 0.018 kg in controls. The weight gains during GD 10-20 were 67-77% and 11-43% of controls at 250 and 400 mg/kg/day, respectively. An increased incidence of the formation of 13^{th} rib was observed at 400 mg/kg/day. The incidence of this finding on fetuses/litter basis was 2.7, 3.9, 4.1 and 5.3 at 0, 100, 250 and 400 mg/kg/day, respectively. The incidence of fetuses at 40 mg/kg/day with this finding was statistically significant. Therefore, this finding was considered to be treatment-related. The increase in the number of resorptions at 400 mg/kg/day was caused by the resorption of an entire litter. At 400 mg/kg/day there was also an increased incidence of abortions.

The maternal toxicity **LOAEL** of Propiconazole in the rabbit is 250 mg/kg/day, based on reduced maternal body weight gains and decreased food consumption during the dosing period. The maternal toxicity **NOAEL** is 100 mg/kg/day.

The developmental toxicity **LOAEL** was 400 mg/kg/day based on increased incidence of fetuses/litters with 13^{th} rib and increased abortions. The developmental toxicity **NOAEL** was 250 mg/kg/day.

Additional data in response to deficiencies noted during earlier review of the study were subsequently submitted (MRID 40425004) and were found to be satisfactory. The study is now classified

Acceptable and satisfies the guideline requirement for a developmental toxicity study in rabbits [870.3700, §83-3b].

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

Supplement to Document No. 005352 - DER for MRID 00151514 & 00163164 and MRID 93194041: Banner (CGA 64250 technical) 2-Generation Reproduction Study in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: 2-Generation Reproduction Study - Rat; OPPTS 870.3800 [§83-4]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (89.7%)

SYNONYMS: Propiconazole, TILT, Banner

CITATION: Borders, CK; Salmon, CM. 1985. Two-Generation Reproduction Study in Albino Rats with CGA 64250 Technical. Study number 450-1202, Toxigenics, Inc., Decatur, IL. March 12, 1985. MRID 00151514. Unpublished, 1202 pages.

Salamon, C.(1983) Two-generation Reproduction Study in Albino Rats Using CGA-64250 Technical: Study No. 450-1202. MRID 00163164 Unpublished study prepared by ToxiGenics, Inc. 20 p.

Tisdel, M. (1990) Ciba-Geigy Corp. Phase 3 Summary of MRID 00138167 and Related MRIDs 00151514, 00163164. Two-Generation Reproduction Study in Rats: Study # 450-1202. MRID 93194041. Prepared by Toxigenics, Inc. 12 p.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a 2-generation reproduction study (MRID 00151514, 00163164, and 93194041), CGA 64250 technical(89.7% purity, FL-830377) was

administered to groups of 15 male and 30 female Charles river CD rats at dose levels of 0, 100, 500 or 2500 ppm/group (mean doses of 8, 42 and 192 mg/kg/day for F0 males, 9.4, 43, 223 mg/kg/day for F0 females, 9.2, 48, 238 mg/kg/day for F1 males and 10, 52, 263 mg/kg/day for F1 females) in the diet. Test diets were administered to both F0 and F1 generation rats during pre-mating period and throughout gestation and lactation periods.

PARENTAL TOXICITY

No compound-related clinical observations or mortality were reported.

Female body weights in the F_0 and F_1 generation were significantly reduced in the high dose group at most of the body weight intervals(82-94% of the controls, $p<0.05$ and 0.01); body weight gains were also significantly reduced during pre-mating (12 weeks)as well as gestation and lactation periods(77-85% of controls, $p<0.01$). Correspondingly, high dose females also had significantly reduced food intake (83-88% of controls). In the F_0 and F_1 generation male body weights were reduced in the high dose groups compared to controls (not statistically significant); body weight gains in this group was 91-94% of controls for the premating period and during the entire duration of the study (7 months). Food consumption was reduced significantly in high dose F_0 males at week 1 (65% of the control, $p<0.01$) and week 7 (86% of the control, $p<0.01$) and in high dose F_1 males and females at week 2, 6 and 10 (84-88% of controls).

Histological examinations revealed that hepatic "cellular swelling" was significantly increased in mid-dose males and high-dose males and females of the F_0 generation. In the F_1 parental animals, increase in the incidence of this finding was significant for both sexes in the mid- and high-dose groups. The incidence of "hepatic clear-cell change" was significantly increased in F_0 high-dose males, F_1 mid-dose and high-dose males and F_1 high-dose females ($p<0.05$). (A summary of hepatic microscopic findings is attached, Attachment 1).

The **LOAEL** for parental toxicity of CGA-64250 (propinoazole) was considered by the original Dynamac and EPA study reviewers to be 100 ppm (8 mg/kg/day) based on an increased incidence of hepatic clear-cell change at all dose levels. However, the incidence of "hepatic clear cell change" at the 8 mg/kg/day was not statistically significant (See attachment 1). Therefore, the **LOAEL** for parental toxicity is now established at 500 ppm (42 mg/kg/day) and the **NOAEL** for parental toxicity is 100 ppm (8

mg/kg/day).

Reproductive parameters (mating, fecundity, gestation, male and female fertility indices, litter resorptions and gestation duration) were comparable in all groups.

DEVELOPMENTAL TOXICITY

The number and percent of viable pups at birth and surviving through weaning were comparable between the dose groups and controls for both the F_{1a} and F_{1b} litters. In the F_{2a} litters, however, the number of pups delivered, delivered viable and surviving to day 4 of lactation were significantly ($p<0.01$) reduced in the high-dose group. The percentages of high-dose pups delivered viable and surviving to day 4 were also reduced (not statistically significant). The F_{2b} litters of these dams had significantly reduced survival rates (both number and percent of surviving pups) at lactation days 7, 14, and 21.

The mean body weights of high-dose progeny were significantly reduced at days 14 and 21 for pups of both generations (72-81% of controls). Reductions were also significant on days 4 and 7 (except for F_{1b} litters) and at birth (F_{2b} litters only).

At necropsy, no treatment related anomalies, organ weight changes and gross pathology findings were noted in pups.

Histopathological evaluation of selected organs from F_{1b} and F_{2b} progeny revealed significantly ($p<0.01$) increased incidences of hepatic "cellular swelling" in high-dose males and females Attachment 2). This was considered to be a compound related effect.

The **LOAEL** and **NOAEL** for developmental toxicity are at 2500 ppm (192-263 mg/kg/day) and 500 ppm (43-52 mg/kg/day), respectively, based on decreased offspring survival and body weights and an increased incidence of hepatic lesions (cellular swelling) at 2500 ppm.

No deficiencies in the study conduct were reported. This study in the rat is classified as **acceptable/guideline** and satisfies the guideline requirement for a 2-generation reproduction toxicity study [870.3800 (83-4)] in rats.

COMPLIANCE: A signed quality assurance statement, dated March 13, 1985 was presented in the final report.

Attachment 1

Incidence of selected hepatic microscopic findings in parental rats fed CGA -64250 for two generations

Parental Generation	Dose Level (ppm)							
	0		100		500		2500	
	M	F	M	F	M	F	M	F
F_0 Parental Animals								
No. examined	15	30	15	29	15	30	15	30
Clear cell change	0	1	2	1	3	1	14**	1
Cellular swelling	7	4	3	3	13*	6	14**	29**
Bile duct hyperplasia	2	2	1	1	1	1	0	1
F_1 Parental Animals								
No. examined	15	30	15	30	15	30	15	30
Clear cell change	2	2	5	4	8*	7	11**	10*
Cellular swelling	0	0	1	2	5*	15**	15**	29**
Bile duct hyperplasia	0	2	2	1	0	2	0	1

* Significantly different from control value ($p<0.05$)
** Significantly different from control value ($p<0.01$)

Attachment 2

Incidence of hepatic microscopic findings in progeny of rats fed CGA -64250 for two generations

Progeny	Dose Level (ppm)							
	0		100		500		2500	
	M	F	M	F	M	F	M	F
F_{1b} Progeny								
No. examined	10	10	10	10	10	10	10	10
Clear cell change	0	0	0	0	0	0	0	0
Cellular swelling	2	1	1	1	2	2	10**	8**
F_{2b} Progeny								
No. examined	10	10	10	30	10	10	10	10
Clear cell change	0	1	0	0	0	0	1	0
Cellular swelling	0	0	0	0	2	1	10**	9**

** Significantly different from control value ($p<0.01$)

98

Supplement to HED Document No. 003994 - DER for MRID 00116591 and MRID 93194034: CGA 64250 Technical: 21 Day Dermal Toxicity Study - Rabbit. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: 21-Day Dermal Toxicity Study - Rabbit; OPPTS 870.3200 [§82-2]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (90.7% purity)

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

CITATION: Larson, E.; Matthews, R.; Naismith, R.; et al. (1982) 21 Day Dermal Toxicity Study in Rabbits: [CGA-64250 Technical]: PH 430-CG-001-82. Rev. (Unpublished study received Oct 4, 1982 under 100-641; prepared by Pharmakon Research International, Inc., submitted by Ciba-Geigy Corp., Greensboro, NC; CDL:248442-E), MRID 00116591

Gillis, J.; Tisdel, M. (1990) Ciba-Geigy Corp. Phase 3 Summary of MRID 00116591. 21-Day Dermal Study in Rabbit: Study # 430-CG-001-82. Prepared by Pharmakon Research Intern. 12 p., MRID 93194034

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a repeated dose dermal toxicity study (MRID 00116591 and 93194034), groups of 20 New Zealand rabbits received 15 daily dermal applications of 0 (11 males and 9 females), 3 (11 males and 9 females), 30 (10 males and 10 females), or 300 (13 males and 7 females) mg/kg/day propiconazole technical(90.7%, Batch

No. FL-810858) over a 21-day period. The test material was applied on the intact and abraded skin with an impervious cuff for 6 hours for five days a week for three weeks.

There were no treatment-related deaths or signs of systemic toxicity and no treatment-related effects on body weight, food consumption, or opthalmology, hematological and clinical chemistry parameters. One high dose female rabbit died on day 3 following diarrhea, decreased activity and body tone. A male rabbit in the low dose group died on day 23, the day of necropsy. Both deaths were not considered compound-related. Diarrhea was observed in one control female, 2 males and 2 females in the low dose group, and 3 males and 1 female in the mid dose group.

Skin irritations were noted in the 30 and 1000 mg/kg/day groups beginning at day 2 and persisted for the remainder of the study with maximum irritation indexes of 1.0 and 4.1, respectively. Signs of irritation were noted in the 3.0 mg/kg/day group beginning on day 15 in males only with the highest irritation index of 0.3 at day 19.

There were no compound related gross necropsy, organ weight effects or histopathological findings.

There were mild to moderate skin lesions which were dose related in treated animals compared to controls. Hyperkeratosis, acanthosis, mild dilation of blood vessels and mononuclear cells and/or heterophils in the proximal dermis were noted in a dose related manner.

The **LOAEL** for systemic effects was >1000 mg/kg/day (the highest dose tested). The **NOAEL** for systemic effects is 1000 mg/kg/day.

The **LOAEL** for skin effects was 3 mg/kg/day based on mild dermal irritation (Hyperkeratosis, acanthosis, mild dilation of blood vessels and mononuclear cells and/or heterophils in the proximal dermis) at 3 and 30 mg/kg/day and moderate dermal irritation at 1000 mg/kg/day. No **NOAEL** for skin lesions was established.

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

COMPLIANCE: This study predated the GLP Guidelines. A phase 3 summary (MRID 93194034) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

100

Supplement to Document No. 009373 - DER for MRID No. 42050502: CGA 64250 Technical - Subchronic Dietary Toxicity Study in Male Mice. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Toxicity Study - Mouse; OPPTS 870.3100 [§82-1a]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (92% purity)

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

CITATION: Potrepka, RF and Turnier, JC. 1991. Thirteen Week Toxicity Study with CGA 64250 in Male Mice. Study number F-00107, Environmental Health Center, Ciba-Geigy Corp. April 30, 1991. MRID 42050502. Unpublished.

SPONSOR: Ciba-Geigy Corporation (Novartis)

EXECUTIVE SUMMARY:

In a subcronic toxicity study (MRID 42050502) propiconazole administered as CGA 64250 (92.0% purity, batch number FL-850083) was administered to 37 days old Crl:CD-1 (ICR) BR Swiss **male** mice (40/dose) at dietary concentrations of 0, 20, 500, 850, 1450 or 2500 ppm (0, 2.7, 65, 112, 194, 352 mg/kg/day, respectively) for 13 weeks. One group of 10 males/dose was sacrificed after 4 weeks, a second group of 10 males/dose after 8 weeks and the third group of 20 males/dose was sacrificed after 13 weeks. This study was conducted to determine the maximum tolerated dose (MTD).

Twice daily inspections of the animals revealed no clinical signs and mortality attributable to the administration of the test article.

Significant differences in weekly body weights between the control and treated mean body weights were limited to animals in the 2500 ppm group during the first 8 weeks of the study. A significant difference was also observed for the 1450 ppm group after 4 weeks. The mean cumulative body weight gains showed significant decreases ($p < 0.01$) for animals in the 2500 ppm during weeks 1, 2, and 4 (36%, 70%, 70% of the body weight gain of the controls, respectively); by week 8 the decrease in body weight gain was 11%. Although the food consumption at 2500 ppm was comparable to controls, the males at 2500 ppm had lower food efficiency (-0.7% vs 1.4% in controls).

There were no treatment-related eye lesions noted.

Statistically significant (< 0.01) increases in liver weights (absolute:116%-182% of controls, and relative to body weight: 118-194% of controls, and relative to brain weight: 119-192% of control) were found in the male animals at ≥500 ppm at the end of the treatment period. Gross pathology examinations revealed generalized enlargement and focal discoloration of the livers at ≥850 ppm.

Hepatocellular hypertrophy, necrosis and vacuolation of the liver significantly increased at ≥500 ppm at all sacrifice times. In general, the severity of the histopathological lesions was dose related with the highest incidence of mild to moderate lesions occurring in the highest dose groups. None of the lesions were classified as either marked or severe.

Serum cholesterol significantly decreased ($p<0.01$) at ≥850 ppm and serum alanine aminotransferase (a serum enzyme associated with hepatic necrosis) and sorbitol dehydrogenate increased at ≥1450 ppm and ≥850 ppm, respectively. Only liver enzymes were measured.

Hematology was not performed.

The **LOAEL** is 500 ppm (65 mg/kg/day), based on increase in absolute and relative liver weights and histopathological liver lesions (hypertrophy, necrosis, vacuolation) seen at 4, 8 and 13 weeks of sacrifice. The **NOAEL** is 20 ppm (2.7 mg/kg/day).

In the original DER, the reviewers concluded that data do not

support the assignment of an MTD to any of the doses tested in this study, since the histopathological lesions were not severe enough. However, based on the findings of increased liver enzyme levels and liver weights and histopathological changes in the liver (Hepatocellular hypertrophy, necrosis and vacuolation), it is now concluded that an MTD (850 ppm) was established. **This study was conducted in males only.** Together with another subchronic study in male and female mice (MRID 42050501), the study is **Acceptable/Guideline** and it satisfies guideline requirements 870.3100 [§82-1a] for a 90-day feeding study in mice.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

Attachment

Significant Clinical Chemistry Findings in Male Mice

Parameter (units)	Week	Propiconazole Dose Level (ppm)					
		0	20	500	850	1450	2500
Cholesterol (mg/dl)	4	129	121	122	92**	81**	47**
	8	114	117	98	104	58**	57**
	13	122	113	102*	86**	75**	67**
Alanine aminotransferase (U/l)	4	24	26	29	42	56**	86**
	8	24	20	29	30	53**	74**
	13	22	23	25	35	53**	79**
Sorbitol dehydrogenase (U/l)	4	26	30	39	45*	58**	66**
	8	27	24	33	30	47**	59**
	13	22	25	25	31*	45**	58**

Supplement to Document No. 009373 - DER for MRID No. 42050501: CGA 64250 Technical - Subchronic Dietary Toxicity Study in Mice. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Toxicity Study - Mouse; OPPTS 870.3100 [§82-1a]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (92.0%)

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

CITATION: Potrepka, RF and Turnier, JC. 1991. Subchronic Dietary Toxicity Study with CGA 64250 in Mice. Study number F-00098, Environmental Health Center, Ciba-Geigy Corp. April 30, 1991. MRID 42050501. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a subcronic toxicity study (MRID 42050501), propiconazole was administered as CGA 64250 (92.0% purity, batch number FL-850083) to 7-week old Crl:CD-1 (ICR) BR (Swiss) mice (20/sex/dose) at dietary concentrations of 0, 20, 500, or 2500 ppm (0, 2.7, 65, 352 mg/kg/day in males and 0, 3.4, 85, 434 mg/kg/day in females, respectively) for 17 weeks. Two additional groups of **male** mice (20/group) were administered the test material at 850 or 1450 ppm (112, 194 mg/kg/day, respectively).

Twice daily inspections of the animals revealed no clinical signs and mortality attributable to the administration of the test

article.

There were no treatment-related effects on the body weight, body weight gain and food consumption in treated mice.

Ophthalmological examinations of all animals at the termination of the study revealed no treatment-related eye lesions.

Statistically significant increases ($p < 0.01$) in liver weights (absolute: 115%-192% of control, and relative to body weight: 113%-204% or relative to brain weight: 116%-194%) were found in the male animals at ≥500 ppm and in the female mice at the 2500 ppm (179% of control, 184% relative to body weight and 189% relative to brain weight).

Gross pathological examination of the livers from the male mice revealed a significant increase in liver enlargement (≥1450 ppm) and focal discoloration (≥850 ppm). The female mice showed a significant increase in liver enlargement at 2500 ppm; focal discoloration was present at 2500 ppm. The increase in absolute and relative liver weights also correlated well with histopathological (hypertrophy and necrosis) and clinical chemistry (increases in both ALT and AST) findings. Males showed significant decreases ($p<0.01$) in serum cholesterol at ≥ 1450 ppm after 13 weeks and at ≥850 ppm. Significant increase ($p<0.01$)in alanine aminotransferase occurred after 17 weeks in males at ≥ 1450 ppm and in females at 13 and 17 weeks at 2500 ppm. Aspartate aminotransferase increased significantly ($p<0.01$) in females at the 17 week interval at 2500 ppm. Clinical chemistry analysis was limited to liver only. Hematology was not performed.

Male mice showed a dose-related increase in both the incidence and severity of histopathological lesions of the liver, while the females showed significant increases only at 2500 ppm. At 500 and 850 ppm dose levels, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 for animals in the 1450 and 2500 ppm groups, respectively. In females at the 2500 ppm dose, 14/20 showed minimal to mild hypertrophy, while 3/20 were classified as moderate. Necrosis occurred both as scattered individual cell foci and multicellular areas. Necrosis was present in males at 500 ppm with significant increases found at ≥850 ppm. The severity and incidence of the necrosis for males in the 1450 ppm group was minimal for 2/20, mild for 5/20 and moderate for 1/20. At 2500 ppm 7/20 and 5/20 male mice showed minimal and mild necrosis, respectively. For females at 2500 ppm 6/20 showed mild necrosis. Cellular necrosis

in males was minimal for 2/20 at 1450 ppm and 7/20 at 2500 ppm and mild for 5/20 at 2500 ppm.

Vacuolation also occurred as scattered individual foci and multicellular areas. Significant vacuolation was present only in the 2500 ppm group where 2/20, 7/20 and 1/20 showed minimal, mild and moderate vacuolation, respectively. No compound-related effect was found when sections of male livers were stained using Oil Red 0, since nearly all of the sections (including the controls) were stained for microvesicular lipid.

Males appeared to be more sensitive to the test article than females.

The **LOAEL** based on increase in absolute and relative liver weights and histopathological changes (hypertrophy, necrosis) is 500 ppm (65 mg/kg/day) in males and 2500 ppm (434 mg/kg/day) in females. The **NOAEL** is 20 ppm in males (2.7 mg/kg/day) and 500 ppm in females (85 mg/kg/day).

In the original DER, the reviewers concluded that the data do not support the assignment of an MTD to any of the doses tested in this study, since the histopathological changes in the liver were not severe enough. However, based on the increased liver enzyme levels, liver weights and severity of liver histopathological findings noted in both sexes, it is now concluded that the MTD was achieved and therefore, this study is classified **Acceptable/Guideline** and it satisfies guideline requirements 870.3100 [§82-1a] for a 90-day feeding study in mice.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

156

Supplement to Document No. 000789 - DER for MRID No. 00058606, MRID No.93194032: CGA 64250 Technical - Three Month Toxicity Study in Rats. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S Diwan, Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Toxicity Study - Rats; OPPTS 870.3100 [§82-1b]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical (90% purity)

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

CITATION: Sachsse, K; Suter, P; Luetkemeier; *et al*. 1979. CGA 64250 Technical: Three Month Toxicity Study in Rats. Project number 790014, Environmental Health Center, Ciba-Geigy Ltd., Switzerland, August 30, 1979. MRID 00058606, Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058606. 90-Day Toxicity Study in Rats: Propiconazole: Study # 790014. Prepared by Ciba-Geigy Ltd., July 10, 1990. MRID No. 93194032. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a subcronic toxicity study (MRID 00058606 & 93194032), CGA 64250 (Batch No. 35/1 P1, 90.0% purity) was administered to Tif (RAIF) SPF rats, approximately four weeks of age (20/sex/dose) at dietary concentrations of 0, 240, 1200, or 6000 ppm (0, 15.85, 76.08 and 461.73 mg/kg bw/day in males and 0, 16.82, 77.59 and

400.90 mg/kg bw/day in females, respectively) for 13 weeks.

No clinical symptoms nor any signs of local and/or systemic toxicity were observed. The survival and mean food consumption of animals was unaffected by the treatment. The body weight and body weight gain of all males and females at 6000 ppm was significantly decreased from weeks 2-13 (79% and 80% of controls body weight and 75% and 73% of controls body weight gain at week 13 for males and females, respectively). The body weight and body weight gain of the females from the 1200 ppm group was significantly decreased from weeks 9-13 when compared to the control (92% of controls body weight and 89% of the controls body weight gain at week 13). Although there was some statistically significant reduction (2-5%) in body weight gain during the same weeks of the study in the low-dose females, the slight decrease in body weight gain in this group is not considered biologically significant. For all animals in the 6000 ppm groups, absolute organ weights (heart, kidney, and adrenal glands in males; kidneys and heart in females) were decreased and relative organ weights to body weight increased while organ to brain weight ratio mostly decreased.

Ophthalmic, auditory and hematological findings showed no evidence of treatment related effects. Erythrocyte count, hematocrit and hemoglobin concentration were found to be significantly lower in female rats of the high dose group at week 13. The only clinical chemistry findings noted consisted of an increase in alkaline phosphatase activity in the high-dose female rats at week 13 and an increase in the γ-glutamyl transpeptidase activity in male and female rats of the high-dose groups at weeks 4, 8, and 13. Histopathology examination of the spleen of all female rats from the 6000 ppm group showed an increase in hemosiderosis.

The **NOAEL** is considered 1200 ppm in males (76 mg/kg bw/day) and 240 ppm in females (16.82 mg/kg bw/day). The **LOAEL** is 6000 ppm in males (462 mg/kg bw /day) and 1200 ppm in females (77.59 mg/kg bw/day) based on reduced body weight gain.

The study was classified **Acceptable** and satisfies the guideline requirement 870.3100 (82-1a) of a sub-chronic study in rats.

COMPLIANCE: The study predated the GLP guidelines. A phase 3 summary (MRID 93194032) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Toxicity Study - Mouse; OPPTS 870.3100 [§82-1a]

DP BARCODE: D269927 SUBMISSION CODE:S587114
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 (92% purity)

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

CITATION: Hardisty, JF. 1997. Thirteen Week Toxicity Study with CGA 64250 in Male Mice : Reexamination of Liver (Supplement for MRID No. 42050502). Laboratory Test No. F-00107, Experimental Pathology Laboratories, Inc. EPL Study No. 140-081. Novartis Study No. 799-97, November 14, 1997. MRID 45215801. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., Greensboro, NC (Syngenta)

EXECUTIVE SUMMARY:

In this study (MRID 45215801) all liver sections from the subchronic study in CD-1 mice (MRID 42050502) were reexamined by a second pathologist(EPL)to compare the liver lesions with those from a subsequently conducted 18-month oncogenicity in CD-1 mice (MRID 44381401) by resolving differences in terminology and the diagnostic criteria used to score the severity of symptoms. In the subcronic toxicity study (MRID 42050502) propiconazole (CGA 64250: 92.0% purity, batch number FL-850083) was administered to 37 days old Crl:CD-1 (ICR) BR Swiss male mice (40/dose) at dietary concentrations of 0, 20, 500, 850, 1450 or 2500 ppm (0, 2.7, 65, 112, 194, 352 mg/kg/day, respectively) for 13 weeks. One group of 10 males/dose was sacrificed after 4 weeks, a second group of 10 males/dose after 8 weeks and the third group of 20 males/dose was sacrificed after 13 weeks. In the 18-month oncogenicity study (MRID 44381401), CGA 64250 technical (Batch

No. OP.303011, Purity 92.4%) was administered to groups of 80 male CrI: CD-1^{R} (ICR) BR mice in the diet at concentrations of 0, 100, 500, or 850 ppm (0, 11.0, 59.0, and 108 mg/kg/day, respectively). Interim sacrifices were conducted at 9 weeks and 12 months on 10 mice/group, and 10 mice/group were designated for blood chemistry evaluation at weeks -1, 9, 14, 53, and 79, the remaining 50 mice/group were used for the main study.

Reexamination of the liver sections from the subchronic study confirmed the histologic evidence of hepatotoxicity at all dose levels and at all sacrifice intervals (4, 8 and 13 weeks) consisting of hepatocellular hypertrophy, monocelluar necrosis (individual hepatocytes), necrosis (small groups of hepatocytes)and fatty change (vacuolation of the liver). Hepatocelluar hypertrophy was seen in both studies at ≥500 ppm at 9 and 8-week sacrifice. The monocellular necrosis, necrosis and fatty changes, were seen ≥1450 ppm in the subchronic study at 9 week sacrifice while the same findings in the 18-month study were seen at 850 ppm (the highest dose tested) at the comparable 8 week sacrifice.

It was concluded by the study author that male mice in the 18-month oncogenicity study were more sensitive to the hepatotoxic effects of CGA-64250 because effects seen at 850 ppm, the dose that caused tumor induction in the 18 month study, showed presence of fatty change, moncellular necrosis and necrosis (at 9 weeks) which were not seen in the 13-week study at the same point (at 8 weeks). This finding does not change the overall NOAEL and LOAEL of 20 and 500 ppm, respectively (2.7 and 65 mg/kg/day, respectively) observed in the original study.

This study is **Acceptable/non-Guideline** and is **Acceptable** with the guideline study (MRID 45215801) which satisfied the guideline requirements for subchronic oral toxicity study in rodents (870.3100; 82-1).

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

10

I. **MATERIALS AND METHODS**: These are described in the DER's for the subchronic study (MRID 42050502) and the 18-month oncogenicity study(MRID 44381401) which were reviewed and found acceptable guideline studies.

In the subchronic toxicity study (MRID 42050502) propiconazole as CGA 64250 (92.0% purity, batch number FL-850083) was administered to 37 days old Crl:CD-1 (ICR) BR Swiss male mice (40/dose) at dietary concentrations of 0, 20, 500, 850, 1450 or 2500 ppm (0, 2.7, 65, 112, 194, 352 mg/kg/day, respectively) for 13 weeks. One group of 10 males/dose was sacrificed after 4 weeks, a second group of 10 males/dose after 8 weeks and the third group of 20 males/dose was sacrificed after 13 weeks. Livers from all animals were evaluated for histopathology.

In the 18-month oncogenicity study (MRID 44381401), CGA 64250 technical (Batch No. OP.303011, Purity 92.4%) was administered to groups of 80 male CrI: CD-1^{r} (ICR) BR mice in the diet at concentrations of 0, 100, 500, or 850 ppm (0, 11.0, 59.0, and 108 mg/kg/day, respectively). Interim sacrifices were conducted at 9 weeks and 12 months on 10 mice/group, and 10 mice/group were designated for blood chemistry evaluation at weeks -1, 9, 14, 53, and 79, the remaining 50 mice/group were used for the main study. Liver sections from all animals from the 9- and 52-week interim sacrifices and terminal sacrifice at 18 months were examined microscopically.

II. HISTOPATHOLOGICAL EXAMINATION

A. SUBCHRONIC STUDY

In the original study, livers from all animals at all sacrifice times were evaluated for histopathology. The incidences of hepatocellular hypertrophy, necrosis and vacuolation of the liver significantly increased at ≥500 ppm at all sacrifice intervals. The severity of the histopathological lesions was dose related. None of the lesions were classified as either marked or severe (MRID 42050502).

B. 18-MONTH ONCOGENICITY STUDY

In the original study, liver sections from all animals from the 9- and 52-week interim sacrifices and terminal sacrifice at 18 months were examined microscopically. Hepatotoxicity was evident after 9 weeks of treatment at ≥500 ppm as hepatocellular hypertrophy, necrosis and

fatty change. The NOAEL is 100 ppm (11.0 mg/kg/day) for males. There was a treatment related increase in hepatocellular adenoma incidences (20 %, $p<0.05$) and total hepatocellular neoplasia (adenomas and carcinomas) of 24%, $p<0.05$, in the liver of animals at the 850 ppm exposure level when compared to controls with a 2% incidence of adenomas and a 4% incidence of total neoplasia (adenomas and carcinomas).

C. HISTOPATHOLOGICAL REVALUATION

Liver sections from the 18-month study were initially examined by the study pathologist, then were reevaluated by a Novartis (Syngenta) reviewing pathologist and subsequently by an external microscopic peer reviewer, Dr. Jerry F. Hardisty (EPL, inc.). Dr. Hardisty's reevaluation included review of all diagnosis from the livers from all male mice in all groups using coded animal numbers.

Dr. Hardisty then compared the 9-week sacrifice histopathologic data from the 18-month oncogenicity study to the 13-week study histopathologic data. He observed differences in **terminology** for the histopathologic changes and differences in the **diagnostic criteria used to score the severity** of each change. The grading scale used by the 13-week study pathologist for scoring the relative severity of a change was 1-5 and the study pathologist for the 18-month study used a scale of 1-3. Different terminology was used for similar changes such as **cytoplasmic vacuolation** in the 13-week study and **fatty change** in the 18-month study to diagnose **intracellular lipid accumulation** in the liver. **To resolve these differences from both studies, Dr. Hardisty reexamined the liver sections from the 13-week study** in an uncoded manner using the same terminology and diagnostic criteria and scoring criteria for the severity of nonneoplastic lesions used in the external peer review of the histopathology data from the 18-month oncogenicity study as described below:

112

Terminology	Diagnostic Criteria
Hepatocellular Hypertrophy	Enalrged hepatocytes with very pale eosinophilic cytoplasm
Fatty Change	Slight amounts of small-sized fatty vacuoles in the centrilobular region of the liver
Monocellular Necrosis	Necrosis of individual hepatocytes
Necrosis	Necrosis of small groups of hepatocytes
Severity of Nonneoplastic Lesions Scoring Criteria	
Grade 1 (Minimal)	Histopathologic change that is a noticeable but not a prominent feature of the tissue
Grade 2 (Moderate)	Histopathologic change that is a prominent but not dominant feature of the tissue
Grade 3 (Severe)	Histopathologic change that is a dominant feature of the tissue

III. RESULTS

A. SUMMARY OF MICROSCOPIC FINDINGS

The histopathological findings of the reexamination of the liver sections from the 13-week study are summarized in Table 1. The histological changes in the liver consisted of hepatocellular hypertrophy, fatty change, monocellular necrosis and necrosis.

B. HEPATOCELLUALR HYPERTROPHY

The incidence and severity of hepatocellular hypertrophy in male mice administered CGA-64250 seen at all sacrifice times were dose related. Histologically, it consisted of enlargement of the centrilobular hepatocytes due to an increased amount of pale eosinophilic cytoplasm. Its severity ranged from minimal to moderate in mice given 500 and 850 ppm and

113

moderate to severe in mice given 1450 and 2500 ppm of the test material in the diet. It should be noted that in the original evaluation of the study pathologist, none of the lesions were classified as either marked or severe (MRID 42050502).

C. FATTY CHANGE

The incidence of the fatty change was increased in male mice at ≥1450 ppm of dietary administration of CGA-64250 at all sacrifice times. Its severity was mostly minimal to moderate in the two highest doses. Only one animal at the highest dose at 4 and 13 weeks sacrifice each, showed severe fatty change in the liver cells. The change was described as "small round, clear, intracytoplasmic vacuoles within the hepatocytes" and it was "scattered multifocally in the liver with no specific lobular distribution".

D. NECROSIS

Two types of liver necrosis were recognized: monocellular necrosis and necrosis. **Monocellular necrosis**, generally not associated with cellular infiltrates or other changes in the surrounding hepatic parenchyma, consisted of individual hepatocytes scattered focally or multifocally throughout the hepatic parenchyma. Their nuclei were either pyknotic or undergoing karyorrhexis and the cell cytoplasm stained more eosiophilic than the surrounding normal cells. In the second pattern of necrosis, diagnosed as "**necrosis**" and characterized by focal necrosis of small groups of hepatocytes which occurred near the margin of the affected lobe of the liver and were accompanied by an infiltration of inflammatory cells or hemorrhage at the margins of the necrotic areas. There was an increased incidence and/or severity of monocellular necrosis and necrosis at ≥850 ppm dietary levels of CGA-64250 at all sacrifice intervals (Table 1).

E. OTHER MICROSCOPIC FINDINGS

Other changes occurred in the liver of control and treated animals and were considered to be not related to treatment. Multifocal infilitrations of lymphocytes and macrophages (histiocytes) occurred frequently (lymphohistiocytic infiltration, Table 1). Other

infrequent changes were pigmentation within Kupffer cells lining the hepatic sinusoids and for mineralization within the hepatic parenchyma.

Table 1. Incidence and severity of hepatoxic effects of 4, 8, and 13 weeks dietary administration of CGA-64250 in CD-1 male mice[1)]

Dose PPM	Hepatocellular. Hypertrophy	Monocellular Necrosis	Necrosis	Fatty Change	Lymphohistiocytic Infiltration
4 Week Sacrifice					
0	0/10	5/10 (5,0,0)[2)]	1/10 (1,0,0)	0/10	6/10
20	1/10 (1, 0, 0)	1/10 (1, 0, 0)	0/10	0/10	3/10
500	10/10 (7, 3, 0)	4/10 (4, 0, 0)	1/10 (1, 0, 0)	0/10	3/10
850	9/10 (3,6,0)	7/10 (7,0, 0)	3/10 (1, 2, 0)	0/10	3/10
1450	10/10 (0, 2, 8)	9/10 (6, 3, 0)	3/10 (3, 0, 0)	2/10 (1, 1, 0)	1/10
2500	9/10 (0, 2, 7)	9/10 (0, 5, 4)	7/10 (3, 4, 0)	7/10 (3, 3, 1)	3/10
8 Week Sacrifice					
0	0/10	6/10 (6, 0, 0)	0/10	0/10	3/10
20	0/10	4/10 (4, 0, 0)	0/10	0/10	4/10
500	8/10 (3, 4, 1)	8/10 (6, 2, 0)	1/10 (0, 1, 0)	1/10 (1,0, 0)	6/10
850	10/10 (0, 7, 3)	4/10 (3, 1, 0)	0/10	0/10	3/10
1450	10/10 (0, 5, 5)	9/10 (7, 2, 0)	5/10 (2, 2, 1)	4/10 (3, 1, 0)	1/10
2500	10/10 (0, 0, 10)	9/10 (4, 4, 1)	6/10 (4, 2, 0)	8/10 (4, 4, 0)	2/10
13 Week Sacrifice					
0	0/20	9/20 (9, 0, 0)	0/20	0/20	12/20
20	1/20 (1, 0, 0)	6/20 (6, 0, 0)	0/20	1/20 (1, 0, 0)	9/20
500	8/20 (7, 1, 0)	5/20 (5, 0, 0)	1/20 (1,0 ,0)	1/20 (1, 0, 0)	7/20
850	20/20 (0, 19, 1)	13/20 (12, 1, 0)	3/20 (1, 2, 0)	3/20 (3, 0, 0)	10/20
1450	20/20 (0, 0, 20)	18/20 (12, 5, 1)	6/20 (4, 2, 0)	7/20 (4, 3, 0)	10/20
2500	20/20 (0, 0, 20)	20/20 (7, 10, 3)	6/20 (5, 1, 0)	16/20 (8, 7, 1)	8/20

[1)] Data reproduced from Tables 3, 4, 5 and 6 of Study Report MRID 45215801
[2)] number of animals exhibiting the effect/total number of animals examined. Numbers in parenthesis are the number of animals with varying degree of hepatotoxiciy (mild, moderate, severe)

15

E. COMPARISON OF THE 13 WEEK STUDY HISTOPATHOLOGICAL REEVALUTION WITH THE 18 MONTH ONCOGENICITY STUDY

The primary purpose of the reexamination of the liver sections from the 13 week study was to compare the 8 week sacrifice to the 9 week sacrifice in the 18 month oncogenicity study using the same terminology and diagnostic criteria. The results of this comparison are presented in Table 2. Qualitative similarities in the histological lesions were seen in both studies. These are hepatocellular hypertrophy, fatty change, moncellular necrosis and necrosis. **Hepatocellular hypertrophy** was increased over controls in both studies at 500 and 850 ppm. For **monocelluar necrosis**; the background incidence in the subchronic study was much higher than in the 18-month study (6/10 vs 0/10). In the subchronic study, this effect was treatment related at ≥1450 ppm while in the 18-month study, it was seen at 850 ppm (the highest dose tested). However, necrotic lesions (**necrosis**) background incidence was much lower in the subchronic study (0/10 vs 2/10) and a treatment related effect in the subchronic study was seen at ≥1450 ppm while in the 18-month study, it was seen at 850 ppm (the highest dose tested). **Fatty change** incidence in mouse livers of the subchronic study was seen at ≥1450 ppm while in the 18-month study, it was seen at 850 ppm (the highest dose tested).

It was concluded by the study author that male mice in the 18-month oncogenicity study were more sensitive to the hepatotoxic effects of CGA-64250 at 9 weeks than the mice in the 13 week study at nearly similar sacrifice time of 8 weeks. This conclusion did not (and does not) change the overall NOAEL and LOAEL of 20 and 500 ppm, respectively observed in the original study.

This study is **Acceptable/non-Guideline.**

16

Table 2. Comparison of Liver Histopathology Results from the 8-week Sacrifice from the 13-week Subchronic Toxicity Study with the 9-week Sacrifice from the 18-Month Oncogenicity Study[a)]

Dietary Dose Level (ppm)	Hepatocellular Hypertrophy		Moncellular Necrosis		Necrosis		Fatty Change	
	Subchr.	Onco.	Subchr.	Onco.	Subchr.	Onco.	Subchr.	Onco.
0	0/10	0/10	6/10	0/10	0/10	2/10	0/10	0/10
20	0/10		4/10		0/10		0/10	
100		0/10		0/10		3/10		2/10
500	8/10	6/10	8/10	1/10	1/10	3/10	1/10	2/10
850	10/10	10/10	4/10	3/10	0/10	5/10	0/10	9/10
1450	10/10		9/10		5/10		4/10	
2500	10/10		9/10		6/10		8/10	

[a)]Reproduced from Table 7 of Study Report MRID 45215801

Supplement to Document No. 000789 - DER for MRID No. 00058607, 93194033: CGA 64250 Technical - Three Month Toxicity Study in Dogs. This supplement provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Abdallah Khasawinah, Ph.D. A. Khasawinah, Date 02-21-02
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D. S. Diwan Date 02-26-02
Reregistration Branch 4 (7509C)

TXR # 0050446

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Toxicity Study - Dogs; OPPTS 870.3100 [§82-1b]

DP BARCODE: D272339 SUBMISSION CODE:S591835
P.C. CODE:122101 TOX. CHEM. NO.:323EE

TEST MATERIAL (PURITY): CGA-64250 technical (88.0% purity)

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

CITATION: Sachsse, K; Suter, P; Luetkemeier; *et al.* 1979. CGA 64250 Technical: Three Month Toxicity Study on Dogs. Project number 785751, Ciba-Geigy Ltd., Switzerland, August 9, 1979. MRID No. 00058607, Unpublished.

Gillis, J; Tisdel, M. 1990. Phase 3 Summary of MRID 00058606. 90-Day Toxicity Study in Dogs: Propiconazole: Study # 785751. Prepared by Ciba-Geigy Ltd., July 10, 1990. MRID No. 93194033 Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY:

In a sub-chronic toxicity study (MRID 00058607, 93194033), CGA 64250 technical(88.0% purity, batch number 35/5) was administered to pure-bred Beagle dogs (4/sex/dose) at dietary concentrations of 0, 50, 250, or 1250 ppm (0, 1.25, 6.25, 31.25 mg/kg/day based on a dose conversion factor for dogs of 1 ppm = 0.025) for 13 weeks. The initial age of the dogs was 19-28 weeks and body weights ranged from 7.9-13.0 kg for males and 6.0-11.6 kg for

females. The dogs were housed in kennels equipped with underfloor heating.

Some animals of all groups including controls showed slight to moderate diarrhea during the whole study. Survival, body weight gain, food consumption, clinical chemistry, urinalysis, ophthalmic and auditory examinations and organ weights revealed no treatment related effects.

Necropsy showed that in 3/4 of male dogs from the highest dosage group (1250 ppm), slightly granular surface in the pyloric and propyloric part of the stomach was noted. Apart from this finding no gross anatomical changes were seen neither in treated nor in control dogs. Microscopically, in 3 out of 4 male dogs from the highest dose-group and 1 out of 4 female dogs from the 250 ppm group slightly increased amount of lymphoid follicles in the mucous membrane of the pyloric part of the stomach was seen. However, this was not seen in the high dose females. These histological findings are considered compound-related.

The **LOAEL** is 250 ppm (6.25 mg/kg/day) based on the finding of lymphoid follicles in the mucous membrane of the pyloric part of the stomach. The **NOAEL** is 50 ppm (1.25 mg/kg/day).

The study is classified **Acceptable/Guideline** and satisfies the guideline requirement (870.3150;(82-1b)) for a sub-chronic study in a non-rodent species

COMPLIANCE: The study predated the GLP guidelines. A phase 3 summary (MRID 93194033) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides data confidentiality statement.