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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050439

DATE: January 31, 2002

MEMORANDUM

SUBJECT: ***PROPICONAZOLE*** - Report of the Hazard Identification Assessment Review Committee.

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

THROUGH: Jess Rowland, Co-Chair
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Susan Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

PC Code: 122101

On December 11, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of propiconazole and selected the toxicology endpoints for use as appropriate in dietary, occupational/residential exposure risk assessments. The potential increased susceptibility of infants and children from exposure to propiconazole as required by the Food Quality Protection Act (FQPA) of 1996 was also addressed. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Pamela Hurley, Elizabeth Mendez, David Nixon, Ayaad Assaad, Jess Rowland, Elizabeth Doyle, John Liccione, Virginia Fornillo

Members in absentia were: Jonathan Chen

Data evaluation prepared by: Abdallah Khasawinah, Ph.D., RRB4

Also in attendance were: Ray Kent, Sanjivani Diwan, Bonnie Cropp-Kohlligian, Susan Hummel, Pauline Deschamp: RARC Chair

Data Evaluation / Report Presentation:

Abdallah Khasawinah
Toxicologist

I. INTRODUCTION

There is no record of propiconazole being reviewed by the TES or HIARC for toxicology endpoint selection for risk assessment. A Reference Dose Committee (RFD) memo dated 4/21/1987 indicates that a reference dose for chronic oral exposure of 0.02 mg/kg/day was selected. This was based on a chronic one year dietary dog study where the NOAEL was 1.9 mg/kg/day based on mild stomach irritation in males. This RFD was later amended by OHEA and OPP in a memo dated 5/25/1988 to 0.013 mg/kg/day based on amended NOAEL in the dog study of 1.25 mg/kg/day to reflect a standard dose conversion factor for dogs of 1 ppm = 0.025 mg/kg/day.

On December 11, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of propiconazole and selected the toxicology endpoints for use as appropriate in dietary, occupational/residential exposure risk assessments. The potential increased susceptibility of infants and children from exposure to propiconazole as required by the Food Quality Protection Act (FQPA) of 1996 was also addressed. The Committee's conclusions are presented in this report.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD) - Females 13 - 50

Study Selected: Developmental Study - Rat Guideline §83-3a

MRID No.: 40425001

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.

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. This effect was considered to be temporary and not treatment related. No significant treatment-related effects on uterine weights, corpora lutea, live and dead fetuses, fetal weights, and resorption were reported.

The maternal toxicity **LOAEL** of Propiconazole is 300 mg/kg/day, based on severe clinical toxicity. 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 un-ossified 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%) 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 a separate study (MRID 40425002) where imazalil was administered to pregnant rats at 0 or 300 mg/kg/day during the gestation period.

The developmental toxicity **LOAEL** of Propiconazole is 90 mg/kg/day, based on increased incidence of rudimentary ribs, un-ossified sternebrae, as well as increased incidence of shortened and absent renal papillae and increased cleft palate. 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.

Dose and Endpoint Selected for Establishing Acute RfD: NOAEL of 30 mg/kg/day based on developmental toxicity manifested as increased incidence of rudimentary ribs, un-ossified sternebrae, as well as increased incidence of shortened and absent renal papillae.

Comments about Study/Endpoint: The developmental effects are presumed to occur after a single exposure and are appropriate for the population of concern (females 13-50).

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation, 10x for intra-species variability)

Acute RfD = $\frac{30 \text{ mg/kg}}{100}$ = **0.3 mg/kg** (females 13-50)

2.2 Acute Dietary RfD - General Population

Study Selected: Developmental Study - Rat Guideline §83-3a

MRID No.: 40425001

Executive Summary: See 2.1 above

Dose and Endpoint Selected for Establishing Acute RfD: Maternal NOAEL of 90 mg/kg/day based on severe clinical toxicity after one day at 360 mg/kg/day administration of propiconazole.

Comments about Study/Endpoint: This endpoint is appropriate since the severe clinical effects were observed after administration of the test material within one day.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation, 10 x for intra-species variability)

Acute RfD = $\frac{90 \text{ mg/kg}}{100}$ = **0.9 mg/kg** (general pop.)

2.3 Chronic RfD

Study Selected: Chronic/Oncogenicity Study - Mice Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: In a 24-month oncogenicity acceptable/guideline study (MRIDs 00129570 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.

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.

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).

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: This dose is appropriate since effects occurred after chronic exposures. Liver toxicity was also reported at similar doses in other chronic toxicity studies. In an 18-month oncogenicity study in mice, the NOAEL for liver toxicity was 11 mg/kg/day and the LOAEL 59 mg/kg/day). In a 24-month feeding study in rats, the NOAEL for liver toxicity was 18 mg/kg/day and the LOAEL 96 mg/kg/day). In 2-generation reproduction study in rats, the NOAEL for liver toxicity was 8 mg/kg/day and the LOAEL 42 mg/kg/day). The HIARC did not select the dog study since stomach irritations were attributed to local effects and not systemic toxicity, and target organ (liver) toxicity seen in mice and rats was not seen in dogs.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation, 10 x for intra-species variability)

$$\textbf{Chronic RfD} = \frac{10\ \text{mg/kg/day}}{100} = \textbf{0.1 mg/kg/day}$$

2.4 Occupational/Residential Exposure

2.4.1 Short-Term (1 - 30 days) Incidental Oral Exposure :

Study Selected : Developmental Study - Rat Guideline §83-3a

MRID No.: 40425001

Executive Summary: See 2.1 above

Dose and Endpoint Selected for Establishing Acute RfD: Maternal NOAEL of 90 mg/kg/day based on severe clinical toxicity within 5 days at 360 mg/kg/day administration of propiconazole.

Comments about Study/Endpoint: The endpoint (clinical signs) are relevant to the population (infants and children) of concern.

2.4.2 Intermediate-Term (1-6 Months) Incidental Oral Exposure

Study Selected: Chronic/Oncogenicity Study - Mice — Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: See 2.3 above.

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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)) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: The HIARC noted that the NOAEL of 2.7 mg/kg/day in the 3-month oral feeding toxicity study in mice is lower than the 10 mg/kg/day selected for this risk assessment. The HIARC did not select the lower NOAEL (2.7 mg/kg/day) because: a) of the wide dose spread between the NOAEL (2.7 mg/kg/day) and the LOAEL (65 mg/kg/day) in that study; b) the LOAEL (50 mg/kg/day) in the selected study is lower than the LOAEL (65 mg/kg/day) of the 3-month mouse oral feeding study; and c) the liver toxicity seen in this study is consistent with that seen in the 18-month mice and 2-generation reproduction studies. Since an oral dose selected, 40% dermal absorption factor should be used for route to route extrapolation.

2.4.3 Dermal Absorption:

Study Selected: Dermal Absorption - Rat — §85-3

MRID No.: 42415701, 00164469, 45345901

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.

The amount of test compound absorbed was directly proportional to the applied dose. The rate of absorption appeared to be saturated at the highest dose level; at the low dose

level, there was a time dependent increase in the amount of compound absorbed. After 24 hours, 57.1, 271 and 3010 $\mu g/cm^2$ (57.13, 27.14 and 30.10% of total dose 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 two studies were classified **Acceptable/guideline** and both satisfy the guideline requirement (870.7600; 85-3) for a dermal absorption study.

Dermal Absorption Factor Selected: 40%

2.4.4 Short-Term Dermal (1 - 30 days) Exposure

Study Selected : Developmental Study - Rat §83-3a

MRID No.: 40425001

Executive Summary: See 2.1 above

Dose and Endpoint for Risk Assessment: Developmental NOAEL of 30 mg/kg/day based developmental toxicity (increased incidence of rudimentary ribs, un-ossified sternebrae and shortened and absent renal papillae).

Comments about Study/Endpoint: This dose/endpoint was selected because of the concern for developmental toxicity which are not evaluated in the 21-day dermal toxicity study. This endpoint covers two populations adults and children. Because an oral dose is used, the dermal absorption factor of 40% should be applied. A 21-day dermal toxicity study in rabbits (MRID 45378201) revealing localized dermal toxic effects at 3 mg/kg/day (the lowest dose tested) was not appropriate for an endpoint since no systemic effects were observed.

2.4.5 Intermediate-Term Dermal (1 - 6 months) Exposure

Study Selected: Chronic/Oncogenicity Study - Mice Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: See 2.3 above.

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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)) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: This dose is appropriate since effects occurred after chronic exposures. Liver toxicity was also reported at similar doses in other chronic toxicity studies. In an 18-month oncogenicity study in mice, the NOAEL for liver toxicity was 11 mg/kg/day and the LOAEL 59 mg/kg/day). In a 24-month feeding study in rats, the NOAEL for liver toxicity was 18 mg/kg/day and the LOAEL 96 mg/kg/day). In 2-generation reproduction study in rats, the NOAEL for liver toxicity was 8 mg/kg/day and the LOAEL 42 mg/kg/day). The HIARC did not select the dog study since stomach irritations were attributed to local effects and not systemic toxicity, and target organ (liver) toxicity seen in mice and rats was not seen in dogs. Since an oral dose is selected, the dermal absorption factor of 40% should be applied.

2.4.6 Long-Term Dermal (>6 months) Exposure

Study Selected: Chronic/Oncogenicity Study - Mice — Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: See 2.3 above.

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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)) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: This dose/endpoint/study was selected for establishing the chronic RfD. Since an oral dose is selected, the dermal absorption factor of 40% should be applied.

2.4.7 Inhalation Exposure

2.4.7.1 Short-term Inhalation Exposure (1 - 30 days)

Study Selected: Developmental Study - Rat — Guideline §83-3a

MRID No.: 40425001

Executive Summary: See 2.1 above

Dose and Endpoint Selected for Risk Assessment: NOAEL of 30 mg/kg/day based developmental toxicity (increased incidence of rudimentary ribs, un-ossified sternebrae and shortened and absent renal papillae).

Comments about Study/Endpoint: An oral dose was selected in the absence of appropriate inhalation toxicity studies.

2.4.7.2 Intermediate-term Inhalation Exposure (1- 6 months)

Study Selected: Chronic/Oncogenicity Study - Mice Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: See 2.3 above.

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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)) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: See 2.3 above.

2.4.7.3 Long-term Inhalation Exposure (>6 months)

Study Selected: Chronic/Oncogenicity Study - Mice Guideline §83-2b

MRID No.: 00129570 and 93194037

Executive Summary: See 2.3 above.

Dose and Endpoint Selected for Establishing Chronic RfD: NOAEL of 10 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)) at 50 mg/kg/day of propiconazole administration.

Comments about Study/Endpoint: See 2.3 above.

2.5 Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

A common toxicological endpoint of concern was identified for short term dermal and inhalation (both routes oral equivalents) and for intermediate and long term oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. These routes can be aggregated for these scenarios for the appropriate population. The short term oral exposure can not be aggregated due to a different toxicological endpoint (maternal toxicity).

2.6 Margins of Exposures for Occupational Exposure Risk Assessments

A MOE of 100 is adequate for both dermal and inhalation routes for occupational exposure risk assessments. The MOEs for residential exposure will be determined by the FQPA Safety Factor Committee.

3. CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID Nos: 00129918, 93194035

Executive Summary: In a 24-month oncogenicity study (MRIDs 00129918, 93194035), propiconazole was administered as CGA 64250 technical (Batch No. P4-6; 87.2-91.9% purity) 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. 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 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 considered 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, 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 cell 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. 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.

Discussion of Tumor Data: Propiconazole was not carcinogenic in rats.

Adequacy of the Dosing for Assessment of Carcinogenicity
The highest dose tested for each sex (2500 ppm) is considered adequate to assess the carcinogenicity of propiconazole.. Body weight gains were significantly reduced (>10%) in both males and females. Hepatotoxic effects were also reported in males and females at this dose.

3.2 Carcinogenicity Study in Mice

MRID No.: 00129570

Executive Summary: See 2.3 above.

Discussion of Tumor Data: 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 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.

Adequacy of Dosing for Assessment of Carcinogenicity

At 2500 ppm the incidence of liver tumors was increased compared to controls, and the effects on survival, liver clinical pathology, histopathology, and body weight and body weight gain were sufficient to indicate that this level was adequate to assess carcinogenicity.

MRID No.: 44381401

Executive Summary: In a more recent 18-month oncogenicity study (MRID 44381401), propiconazole was administered as CGA 64250 technical (Batch No. OP.303011, Purity 92.4%) to groups of 80 male CrI: CD-1^{r}(ICR) BR mice in the diet at concentrations of 0, 100, 500, or 850 ppm. These concentrations resulted in a nominal compound intake for

each concentration level of 0, 11.0, 59.0, and 108 mg/kg/day for control, low-, mid-, and high-dose, 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. No overt clinical signs were noted over the course of the study in any of the treated groups, and survival in all the treated groups was comparable to the control. Body weight and body weight gain were significantly ($p<0.01$) decreased in the 850 ppm group compared to the control group for weeks 18-50. Body weight gain was decreased by up to 10 % (n.s.) in the 500 ppm group compared to the control group. The liver was identified as a target organ based on several toxic effects to this organ. Statistically significant ($p <0.01$) concentration dependent effects consisted of increases in mean liver weight and mean liver to body weight ratios were observed in the high-dose group and increases in these values (n.s.) were also observed in the mid-dose group compared to the control group. At the interim, increases were 32 and 33% at the week 9 sacrifice, 11 and 29 % at the week 53 sacrifice, and 19 and 20% at the terminal sacrifices in the 850 ppm group compared to the control group liver weights and liver to body weight ratios, respectively. The high-dose group mice also were found to have significantly more (61%; $p<0.05$) incidences of enlarged livers compared to the control group. Increased incidences of liver masses and nodules (n.s.) were also observed in the 850 ppm treated animals compared to the controls. Hepatocellular hypertrophy was significantly increased by 86% and 93% ($p<0.01$), respectively in the mid- and high-exposure groups. There was a dose related increase in the incidence of liver necrosis at $\geq$100 ppm at the week 9 sacrifice ($p\leq0.007$), and at the final sacrifice ($p\leq0.003$). There was an increase in the incidences of fatty change, lymphohistiocytic infiltration, and incidence of foci of cellular change in the livers of animals in the high-dose group ($p < 0.05$) but only at the week 9 interim sacrifice. A suggestion of altered metabolic function at $\geq$500 ppm was noted in decreased cholesterol (14% to 24%) at week 14 and at 850 ppm in increased sorbitol dehydrogenase (45%) at week 14. However, the liver enzymes, ASAT, ALAT and ALP were unaffected at the highest dose tested. **The LOAEL is 500 ppm in the diet (59.0 mg/kg/day) for males, based on hepatotoxicity and body weight gain effects observed at the interim and terminal sacrifices. The NOAEL is 100 ppm (11.0 mg/kg/day) for males.** There was a treatment related increase in the incidence of hepatocellular adenoma (20 %, $p<0.05$) and combined hepatocellular adenomas and carcinomas (24%, $p<0.05$) at the 850 ppm exposure level when compared to controls with a 2% incidence of adenomas and a 4% incidence of combined adenomas and carcinomas. Dosing was considered to be adequate based on decrease in body weight gain and hepatotoxic effects seen at 500 and 850 ppm. The percentage adenomas and carcinomas were within the range of the inadequate historical control data submitted with the study report. In the 850 ppm dose group, the combined incidence of hepatocellular tumors was slightly higher (24%) than the upper limit of the historical control range of 22.4% submitted and the concurrent control (4%) was lower than of the lower range of historical controls of 6.0% submitted. The historical controls data were inadequate because the collection dates were not specified and were not collected in the testing facility. This oncogenicity study in the mouse is **acceptable (guideline)** . This study is

acceptable only when considered in conjunction with older oncogenicity study in mice (HED Doc# 004287 and 005352; MRID#073919,250784-250786 and 251237).

Discussion of Tumor Data There was a treatment related increase in the incidence of hepatocellular adenoma (20 %, $p<0.05$) and combined hepatocellular adenomas and carcinomas (24%, $p<0.05$), in male mice at the 850 ppm exposure level when compared to controls with a 2% incidence of adenomas and a 4% incidence of combined adenomas and carcinomas. Based on HED standard statistical analysis, there was a significant dose-related increasing trend, and a significant difference in the pair-wise comparison of the 850 ppm dose group with the controls, for liver adenomas and/or carcinomas combined, both at $p < 0.01$.

Adequacy of Dosing for Assessment of Carcinogenicity

There were no mortalities related to treatment. Body weight and body weight gain were significantly ($p<0.01$) decreased up to 19% in the 850 ppm group compared to the control group for weeks 18-50. Body weight gain was decreased by up to 10 % (n.s.) in the 500 ppm group compared to the control group. After week 50, the treated groups seemed to recover and remained comparable to controls in body weight and weight gain throughout the remainder of the study. Food consumption and food consumption ratios were unaffected by the administration of the test substance as they both remained comparable to the control group throughout the study. Dosing was considered to be adequate based on the body weight gain and hepatotoxic effects seen at 500 and 850 ppm.

3.3 Classification of Carcinogenic Potential

The HED Carcinogenicity Peer Review Committee (CPRC) classified propiconazole as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the reference Dose (RfD) approach should be used for quantification of human risk (HED Doc. No. 009771, April 15, 1992 meeting).

Mechanistic studies have been conducted recently (1998 & 1999) demonstrating that propiconazole is a strong phenobarbital-type inducer of xenobiotic metabolizing enzymes in the mouse (MRID 45215803) and causes hepatocellular proliferation in a manner similar to that of phenobarbital (MRID 345215802)

4. MUTAGENICITY

Propiconazole was not mutagenic in seven different tests as shown in this table.

GL #	MRID	Study Type	Results and Classification
84-2 870-5100	00058601	Bacterial reverse mutation 25-2025 µg/plate Sept. 17, 1979	Negative in Salmonella strains with or without S-9 activation. **Unacceptable**: test material purity not specified, not tested up to cytotoxic dose.
84-2 870-5300	00133349	In vitro cell transformation assay (BALB/3T3), technical,# Op. 103119; purity 90.7% 1.16-18.5 µg/ml August 10, 1982	Did not cause a measurable increase in transformation of BALB/T3 cells. Highest dose produced 25% reduction in colony forming ability. **Acceptable/guideline**
84-2 870-5385	00058603	In vivo micronucleus test (bone marrow chromosomal aberration) - Chinese hamsters; Tech. # INA 35/1 P1, purity 90.0% 0, 251, 502 or 1004 mg/kg	Negative for induction of micronuclei in bone marrow cells at all levels tested. **Acceptable/guideline**
84-2 870-5550	00133347	Unscheduled DNA synthesis in human fibroblasts, Tech. # Op. 103119, Purity 90.7% August 12, 1982	Negative for inducing Unscheduled DNA Synthesis at concentrations up to and including 9.32 µg/ml. Highest dose tested to allow at least 25% cell viability **Acceptable/guideline**
84-2 870-5550	00133348	Unscheduled DNA synthesis in primary rat hepatocytes, technical,# Op. 103119; purity 90.7% August 12, 1982	Negative for inducing Unscheduled DNA Synthesis at concentrations up to and including 83.5 µg/ml. Highest dose tested to allow at least 25% cell viability **Acceptable/guideline**
84-2 870-5575	00133343	Mitotic gene conversion assay (*Saccharomyces cerevisiae*), technical,# Op. 103119; purity 90.7% August 19, 1982	No increase in convertants or revertants (did not induce mutation) tested at 10, 30, 90 or 270 µg/ml with or without activation. Concentrations of ≥30 µg/ml had inhibitory effect on yeast cell growth. **Acceptable/guideline**
84-2 5450	00058602	Dominant lethal assay in mice: 165 or 495 mg/kg single dose oral gavage. Tech. # INA 35/1 P1, purity 90.0% October 31, 1979	No evidence of dominant lethal effects was observed in the progeny of mice treated with propiconazole. **Acceptable/guideline**

5. FQPA CONSIDERATIONS

5.1. Neurotoxicity:

No neurotoxicity studies are available. No evidence of neurotoxicity was apparent in any of the available studies.

5.2 Developmental Toxicity

5.2.1 Rabbit:

In a developmental toxicity study (MRID 00265796), CGA 64250 technical(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. Additional data to respond to noted deficiencies in the study were subsequently submitted (MRID 40425004) and were found satisfactory. The study is classified **Acceptable/Guideline**.

5.2.2 Rat:

MRID No.: 40425001. See 2.1 above.

MRID 40425002. In an **acceptable/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 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 0/1222 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) discussed in Section 2.1.

5.3 Reproductive Toxicity:

In an **acceptable/guideline** 2-generation reproduction study (MRID 00151514), CGA 64250 technical (89.7% purity, FL-830377) was administered to 15 male and 30 female Charles river CD rats at dose levels of 0, 100, 500 or 2500 ppm (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 ($p<0.05$). The **LOAEL** for parental toxicity of CGA-64250 (proinoazole) 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. 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.

Offspring 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. This was considered to be a compound related effect. The **LOAEL** and **NOAEL** for offspring 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.

5.4 Additional Information from the Literature:

In a published study, propiconazole (provided by Ciba-Geigy as Tilt 100 EC in the form of 10% solution) was administered to groups of pregnant female albino rats (15/dose) at

0, 75.85 or 151.70 mg/kg/day on days 6-15 of gestation (Hassan, MS. 1993. Embryotoxic and teratogenic effects of the organic fungicide tilt in albino rats. Bull. Fac. Pharm., Cairo University 31(3): 459-463). Rats were sacrificed on day 20 of gestation. Postimplantation deaths, resorption sites and dead fetuses were counted. Fetuses were examined for morphological, visceral and skeletal malformations. Propiconazole was fetotoxic at both doses causing significant ($p<0.05$) increased fetal resorptions (8 and 21% at the low and high dose vs 0% in the control), increased fetal deaths (10 and 24% at the low and high doses vs. 2% in the control) and decreased fetal weight). The mean number of stunted fetuses was significantly higher ($p<0.05$) at both doses (1.43 and 3.57 at the low and high dose vs. 0.13 in the control). Incomplete ossification of the skull, caudal vertebrae and digits, extra rib (14th rib) and missing sternbrae. Malformations of the lung and kidneys were reported. No maternal toxicity was reported at either dose. The **LOAEL** for developmental toxicity in this study is 76 mg/kg/day (the lowest dose tested). **NOAEL** is not established.

A report from Australia (HED Doc. No. 005638) on the incidence of major congenital malformations in the Coffs Harbour Region of New South Wales stated that "although there was a temporal association between the widespread use of a new fungicide (Tilt: propiconazole) in Coffs Harbour and the period of organogenesis of the cluster of infants with cleft lip and palate, there was no direct evidence to implicate this, or any other, chemical pesticide as the cause of these congenital malformations". There have been no follow up studies of this case.

5.5 Determination of Susceptibility:

In rats, there was evidence for quantitative susceptibility; developmental effects (increase in rudimentary ribs, unossified sternbrae, shortened/absent papillae were seen at a lower dos than that caused maternal toxicity. No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rabbits or following pre/post exposure to rats. Fetal offspring toxicity was seen at higher doses than those causing maternal/parental toxicity.

5.6 Determination of the Need for Developmental Neurotoxicity Study:

There is no evidence of neurotoxicity, neuropathology or abnormalities in the development of the fetal nervous system from the available toxicity studies conducted with propiconazole. However, neurotoxic effects (ataxia, lethargy, salivation, rales) were noted in pregnant rats administered high propiconazole doses (360 mg/kg/day) during gestation period. In view of the neurotoxic effects observed in pregnant rats, the HIARC determined that an acute neurotoxicity (ACN) study is required. A DNT study is not required at this time, but will be reconsidered when the required ACN is conducted and submitted to the Agency.

6. HAZARD CHARACTERIZATION

The data base for propiconazole is adequate for hazard characterization. Propiconazole has low to moderate toxicity in experimental animals by the oral (Category III), dermal (Category III) and inhalation routes (Category IV), is moderately irritating to the eyes (Category III), and minimally irritating to the skin (Category IV) and it is not a dermal sensitizer. Propiconazole is readily absorbed by the rat skin with a 40% absorption rate within 10 hours of application.

The primary target organ for propiconazole toxicity in animals is the liver. Increased liver weights were seen in mice after subchronic or chronic oral exposures to propiconazole at doses >50 mg/kg/day. Liver lesions such as vacuolation of hepatocytes, ballooned liver cells, foci of enlarged hepatocytes, hypertrophy and necrosis are characteristic of propiconazole toxicity in rats and mice. Mice appear to be more susceptible to its toxicity than rats. Decreased body weight gain in experimental animals was seen in subchronic, chronic, developmental and reproductive studies. Dogs appeared to be more sensitive to the systemic toxicity of propiconazole as manifested by stomach irritations at 6 mg/kg/day and above.

In rabbits, developmental toxicity occurred at a far greater dose than the maternal toxic dose, while in rats, developmental toxicity occurred at much lower doses than maternal toxic doses. Increased incidences of rudimentary ribs occurred in rat and rabbit fetuses. Increased cleft palate malformations were noted in two studies in rats. In one published study in rats developmental effects (incomplete ossification of the skull, caudal vertebrae and digits, extra rib (14^{th} rib) and missing sternbrae, malformations of the lung and kidneys) were reported at doses that were not maternally toxic.

In the two generation reproduction study in rats, offspring toxicity occurred at much lower dose than the parental toxic dose suggesting lower susceptibility of the offspring to the toxic doses of propiconazole.

Propiconazole was negative for mutagenicity in seven submitted studies. It caused proliferative changes with or without pretreatement with an initiator, in the rat liver similar to phenobarbital, a known liver tumor promoter. Liver enzyme induction studies with propiconazole in mice demonstrated that propiconazole is a strong phenobarbital type inducer of xenobiotic metabolizing enzymes. Hepatocellular proliferation studies in mice suggest that propiconazole induces cell proliferation followed by treatment related hypertrophy in a manner similar to the known hypertrophic agent phenobarbital.

Carcinogenicity studies in mice indicated that propiconazole was carcinogenic to male mice based on significant increase in the incidence of hepatocelluar adenomas and adenomas/carcinomas combined. Propiconazole was not carcinogenic to rats in the study provided. The HED Carcinogenicity Peer Review Committee (CPRC) classified propiconazole as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the reference Dose (RfD) approach should be used for quantification of human risk (HED Doc. No. 009771, April 15, 1992 meeting).

7. DATA GAPS

28-Day Inhalation - Rat
Acute Neurotoxicity - Rat
Bacterial Reverse Mutation Assay (Ames Test)

8. ACUTE TOXICITY

Acute Toxicity of Propiconazole

Guideline No.	Study Type	MRID #	Results	Toxicity Category
81-1	Acute Oral - rat	00058591	LD_{50} =1517 mg/kg	III
81-2	Acute Dermal-rabbit	00058596	LD_{50} = >4000 mg/kg	III
81-3	Acute Inhalation - rat	41594801	LC_{50} = >50.84 mg/L	IV
81-4	Primary Eye Irritation	00058597	Corneal opacity reversed in 72 hours	III
81-5	Primary Skin Irritation	00058598	No irritation	IV
81-6	Dermal Sensitization	00058600	Non sensitizer	-

9. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION -PROPICONAZOLE

The propiconazole doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary Females 13-50	NOAEL = 30 mg/kg/day	Developmental toxicity: increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae.	Developmental toxicity study - rats
	Acute RfD = 0.3 mg/kg		
Acute dietary General Population	NOAEL = 90 mg/kg/day	Severe maternal toxicity: ataxia, coma, lethargy, prostration, audible and labored respiration, salivation and lacrimation	Developmental toxicity study - rats
	Acute RfD = 0.9 mg/kg		
Chronic Dietary	NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice
		Chronic RfD = 0.1 mg/kg/day	
Incidental Short Term (Oral)	Developmental NOAEL = 30 mg/kg/day	Developmental toxicity: increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae.	Developmental toxicity study - rats
Incidental Intermediate Term (Oral)	Oral NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice
Short-Term* (Dermal)	Developmental NOAEL = 30 mg/kg/day	Developmental toxicity: increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae.	Developmental toxicity study - rats
Intermediate-Term* (Dermal)	Oral NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice

Long-Term (Dermal)*	Oral NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice
Inhalation** Short-Term	Developmental NOAEL = 30 mg/kg/day	Developmental toxicity: increased incidence of rudimentary ribs, cleft palate malformations (0.3%) unossified sternebrae, as well as increased incidence of shortened and absent renal papillae.	Developmental toxicity study - rats
Inhalation** Intermediate-Term	Oral NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in ms and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice
Inhalation** Long-Term	Oral NOAEL = 10 mg/kg/day	Liver toxicity (increased liver weight in males and increase in liver lesions (masses/raised areas/ swellings/nodular areas mainly)	24 month oncogenicity study - mice

* Since oral NOAEL are selected, a dermal absorption factor of 40% is applied in risk assessments.

** 100 % inhalation absorption rate should be used for risk assessments.

13544

038261

Chemical:	**1H-1,2,4-Triazole, 1-((2-(2,4-dichloroph**
PC Code:	**122101**
HED File Code	**21100 HIARC**
Memo Date:	**01/31/2002**
File ID:	**TX050439**
Accession Number:	**412-02-0281**

HED Records Reference Center
05/10/2002