CASWELL FILE

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

009373

MAR 23 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: Review of the following toxicity studies: "Subchronic Dietary Toxicity Study with CGA 64250 in Mice" and "13-Week Toxicity Study with CGA 64250 in Male Mice"

Caswell No: 323EE

MRID No's: 420505-01 (90-day oral-mouse, 82-1)
420505-02 (90-day oral-mouse, 82-1)

TO: Sidney Jackson, PM-21
Registration Division (H7505C)

FROM: Robert F. Fricke, Ph.D. Robert F. Fricke 17 Mar 92
Toxicology Branch II, Section IV
Health Effects Division

THRU: Elizabeth Doyle, Ph.D. E.A. Doyle 3/18/92
Toxicology Branch II, Head Section IV
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 3/18/92
Chief, Toxicology Branch II

Registrant: Ciba-Geigy Corp., Agricultural Division
P.O. Box 18300, Greensboro, NC 27419

Action Requested: Review of toxicity studies

CONCLUSIONS:

1. These two studies were submitted as supplemental data to support lowering of the MTD for propiconizole. The data presented in these studies do not support reassignment of the MTD value of 2500 ppm. The MTD was used in a previously submitted oncogenicity study upon which the $Q^*$ is based.

(1)

2. 420505-01 (90-day oral - Mouse, 82-1)

Male and female Crl mice were given the test material, incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm, for 17 weeks. Although histopathological lesions were noted, they were not severe enough to support the assignment of an MTD to any of the doses tested.

3. 420505-02 (90-day oral - Mouse, 82-1)

In this study male Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm for 13 weeks. Again, based upon the severity of the lesions, the data did not support the assignment of an MTD to any of the doses tested.

One-liner

CITATION

90-day oral toxicity study in mice, Ciba-Geigy Corp., Agricultural Division, F-00098, 30 April 1991.

MATERIAL: Propiconizole, CGA-64250

EPA ACCESSION No.: 420505-01

RESULTS: Male and female Crl mice were given the test material, incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm, for 17 weeks. Although histopathological lesions were noted, they were only moderate in severity and not considered life threatening at any dose tested. NOEL: 20 ppm (male and female); LOEL: 500 ppm (male), 2500 ppm (female).

CORE Grade/Doc No.: Supplementary

One-liner

CITATION

90-day oral toxicity study in male mice, Ciba-Geigy Corp., Agricultural Division, F-00107, 30 April 1991.

MATERIAL: Propiconizole, CGA-64250

EPA ACCESSION No.: 420505-02

RESULTS: Male Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm for 13 weeks. Although histopathological lesions were noted, they were only moderate in severity and not considered life threatening at any dose tested. NOEL: 20 ppm; LOEL: 500 ppm.

CORE Grade/Doc No.: Supplementary

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 13 Mar 92
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D. E.A. Doyle 3/18/92
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 90-day oral - Mouse (82-1) TOX. CHEM. NO.: 323EE

MRID NO.: 420505-01

TEST MATERIAL: Propiconazole

SYNONYMS: CGA-64250

STUDY NUMBER: F-00098

SPONSOR: Ciba-Geigy Corp., Agricultural Division
P.O. Box 18300, Greensboro, NC 27419

TESTING FACILITY: Ciba-Geigy Corp., Environmental Health Center
400 Farmington Avenue, Farmington, CN 06032

TITLE OF REPORT: Subchronic Dietary Toxicity Study with CGA-64250 in Mice

AUTHOR: Robert F. Potrepka and John C. Turnier

REPORT ISSUED: April 30, 1991

CONCLUSIONS: For 17 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively) for males and 0, 20, 500, or 2500 ppm (equivalent to 3.4, 85 or 434 mg/kg/day, respectively) for females.

| | NOEL | LOEL |
|---|---|---|
| Male | 20 ppm (LDT) | 500 ppm (MDT1) |
| Female | 20 ppm (LDT) | 2500 ppm (HDT) |

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

5

A. MATERIALS:

1. Test compound: Propiconazole Description: yellow viscous liquid, Batch #: FL-850083, Purity: 92.0%, Contaminants: List in CBI appendix

2. Test animals Species: Mouse Strain: Crl:CD-1 (ICR) BR (Swiss) Age: 7 weeks Weight (g): 24.6-39.0 (males), 19.7-27.0 (females) Source: Charles River Laboratories, Inc., Raleigh, NC.

B. STUDY DESIGN:

1. Animal assignment: Animals were assigned randomly to test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

| Test Group | Dose in Diet (ppm) | Main Study (17 weeks) | |
|---|---|---|---|
| | | Male | Female |
| Control (CON) | 0 | 20 | 20 |
| Low (LDT) | 20 | 20 | 20 |
| Mid 1 (MDT1) | 500 | 20 | 20 |
| Mid 2 (MDT2) | 850 | 20 | --- |
| Mid 3 (MDT3) | 1450 | 20 | --- |
| High (HDT) | 2500 | 20 | 20 |

2. Diet preparation: Diet was prepared approximately every three weeks and stored at 4°C until used. Samples of treated food were analyzed for homogeneity and concentration within two days of preparation. Homogeneity of the prepared diets was within 1.1 and 12.1 % of the nominal concentration. The concentration of the test article was within the 89.9 to 106.5 % of nominal.

3. Animals received food (Purina Certified Rodent Chow #5002) and water ad libitum.

4. Statistics: Statistical analyses consisted of an initial analysis of variance (ANOVA) followed by the Dunnett's Test if the outcome of the ANOVA was significant. The male body weights and cumulative body weights were first analyzed using the Bartlett's test, followed by ANOVA and Dunnett's Test if significance was found. Trend analyses of the male body weights and cumulative body weights were carried out using the Terpstra-Jonckheere test. The incidence data for histopathology findings were analyzed using the Fisher's exact test with Bonferroni's correction for multiple comparisons to a single control level.

5. Quality assurance was documented by signed and dated GLP and quality assurance statements.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of toxicity, moribundity and mortality.

a. Toxicity: There were no clinical observations attributable to the administration of the test article.

b. Mortality (survival): One male mouse in the 20 ppm group was found dead during week 15 and one unscheduled sacrifice occurred for a male mouse at 850 ppm during week 10. No female mice died during the study.

2. Body weight: Animals were weighed weekly during the 17 week treatment period.

Results: The body weights of the male and female mice were not significantly different from control values throughout the entire study.

Significant findings for body weight gain in male mice are summarized in Table 2, below. Significant differences were noted only during the first two weeks of the study. The female mice did not show any significant differences between the treated groups and the control.

Table 2: Body Weight Gain (g) for Male Mice

| Week of Study | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| 1 | 0.8 | 1.1 | 1.0 | 0.8 | 1.2 | 0.0** |
| 2 | 0.5 | 1.1* | 1.2* | 1.5* | 1.4** | 1.6 |

* $p < 0.05$, ** $p < 0.01$

3. Food consumption and compound intake: Food consumption was determined weekly and mean daily consumption was calculated.

a. Food consumption results: Daily food consumption (g/animal/day) was determined for both male and female mice. The females did not show any significant treatment-related effects. Significant findings for the male mice are summarized in Table 3, below.

Table 3: Food consumption (g/day) by Male Mice

| Week of Study | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| 8 | 5.0 | 5.2 | 5.0 | 4.9 | 5.1 | 5.9** |
| 9 | 4.9 | 5.1 | 4.8 | 4.8 | 5.4* | 5.2 |
| 10 | 4.7 | 4.7 | 4.6 | 4.7 | 4.9 | 5.3* |
| 12 | 4.6 | 4.9 | 4.8 | 4.7 | 5.1* | 5.2* |
| 14 | 4.3 | 4.7 | 4.3 | 4.4 | 4.7 | 4.9** |

* $p < 0.05$, ** $p < 0.01$

b. Food efficiency results: The food efficiency was determined for both male and female mice. Significant findings are summarized in Table 4, below.

6. Urinalysis: Not performed

Table 4: Food Efficiency (percent) (g body weight gain/g food consumed)

| Week of Study | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| **Male** | | | | | | |
| 1 | 1.8 | 2.9 | 2.2 | 2.0 | 3.1 | -0.5* |
| 2 | 1.7 | 3.1* | 3.6** | 4.5** | 3.9** | 4.7** |
| 3 | 3.5 | 1.9* | 1.8** | 0.9** | 1.8* | 0.5** |
| 8 | 2.3 | 1.7 | 3.0 | 3.7* | 1.6 | 0.8* |
| 11 | 2.3 | -0.4** | 2.3 | 1.1 | 2.1 | 1.7 |
| 17 | -1.3 | -1.6 | 0.3* | 0.3* | 2.4** | 2.0** |
| **Female** | | | | | | |
| 1 | 4.9 | 2.4* | 2.0* | --- | --- | 1.5 |
| 3 | 3.0 | 3.7 | 4.3 | --- | --- | 5.3* |
| 15 | 0.4 | 2.0 | 3.4** | --- | --- | 1.5 |

* $p < 0.05$, ** $p < 0.01$

c. Compound intake results: The average daily compound consumption for male and female animals is summarized below in Table 5.

Table 5: Average daily consumption of compound at each dose level for male and female mice.

| Dose Level (ppm) | Compound Consumption (mg/kg/day) | |
|---|---|---|
| | Male | Female |
| 20 | 2.7 | 3.4 |
| 500 | 65 | 85 |
| 850 | 112 | --- |
| 1450 | 194 | --- |
| 2500 | 352 | 434 |

4. Ophthalmological examinations: Examinations were performed on all animals at the termination of the study. No treatment-related eye lesions were observed.

5. Hematology and Clinical Chemistry: Clinical chemistry analyses were performed after 13 weeks of exposure and at the termination of the study. The checked (X) parameters were examined.

a. Hematology: Not performed

b. Clinical Chemistry

Electrolytes
- Calcium
- Chloride
- Magnesium
- Phosphorous
- Potassium
- Sodium

Enzymes
- X Alkaline phosphatase
- Cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- X Serum alanine aminotransferase (SGPT/ALT)
- X Serum aspartate aminotransferase (SGOT/AST)

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- X Cholesterol
- Globulins
- Glucose
- Total Bilirubin
- Triglycerides
- Total Protein

Results: Significant clinical chemistry findings are shown in Table 6, below.

Table 6: Clinical Chemistry Findings

| Analyte (units) | Week of Study | Dose Level (ppm) 0 | 20 | 500 | 850 | 1450 | 2500 |
|---|---|---|---|---|---|---|---|
| **Male** | | | | | | | |
| Cholesterol (mg/dl) | 13 | 120 | 108 | 121 | 108 | 70** | 71** |
| | 17 | 119 | 104 | 105 | 91** | 66** | 67** |
| Alanine Amino-transferase (U/l) | 13 | 52 | 31 | 39 | 43 | 65 | 81 |
| | 17 | 17 | 33 | 28 | 29 | 65** | 128** |
| **Female** | | | | | | | |
| Aspartate Amino-transferase (U/l) | 13 | 67 | 60 | 61 | --- | --- | 68 |
| | 17 | 45 | 47 | 55 | --- | --- | 68** |
| Alanine Amino-Transferase (U/l) | 13 | 27 | 24 | 27 | --- | --- | 64** |
| | 17 | 17 | 20 | 21 | --- | --- | 61** |

** $p < 0.01$

7. Sacrifice and Pathology: Detailed pathological examination was performed on male and female mice in the control and treatment groups. The checked (X) tissues were collected for histological examination; the checked (XX) organs were also weighed.

Digestive system
- Tongue
- X Salivary glands
- X Esophagus
- X Stomach
- X Duodenum
- X Jejunum
- X Ileum
- X Cecum
- X Colon
- X Rectum
- XX Liver
- X Gall bladder
- X Pancreas

Respiratory
- X Trachea
- X Lung
- X Nasal Passages

Cardiovas./Hematol
- X Aorta
- X Heart
- X Bone marrow
- X Lymph nodes
- X Spleen
- X Thymus

Urogenital
- X Kidneys
- X Urinary bladder
- X Testes
- X Epididymides
- X Prostate
- X Seminal vesicle
- X Ovaries
- X Uterus
- X Vagina
- X Cervix

Neurologic
- XX Brain
- X Periph. nerve
- X Spinal cord (3x)
- X Pituitary
- X Eyes (optic nerve)

Glandular
- X Adrenals
- Lacrimal gland
- Mammary gland
- X Parathyroids
- X Thyroids

Other
- X Bone
- X Skeletal muscle
- X Skin
- X Joint
- X Harderian glands
- X Gross lesions

a. Liver weights: At the end of the treatment period, the absolute and relative liver weights were determined. As summarized in Table 7, below, statistically significant

increases were found in the male animals at 500 ppm or higher and in the female mice at the 2500 ppm.

Table 7: Absolute and relative liver weights of male and female mice

| Dose Level (ppm) | Absolute (g) | % of Body Weight | % of Brain Weight |
|---|---|---|---|
| **Male** | | | |
| 0 | 1.445 | 3.961 | 286.3 |
| 20 | 1.408 | 4.108 | 283.8 |
| 500 | 1.660* | 4.486** | 332.2* |
| 850 | 1.792** | 5.131** | 363.0** |
| 1450 | 2.450** | 6.701** | 480.2** |
| 2500 | 2.773** | 8.102** | 555.0** |
| **Female** | | | |
| 0 | 1.177 | 4.182 | 230.6 |
| 20 | 1.267 | 4.533 | 250.9 |
| 500 | 1.215 | 4.414 | 243.9 |
| 2500 | 2.110** | 7.684** | 435.5** |

* $p < 0.05$, ** $p < 0.01$

b. Gross pathology: The only observations of toxicological significance were generalized enlargement and focal discoloration of the livers. The incidence data is presented in Table 8, below.

c. Microscopic pathology

1) Non-neoplastic: Examination of the livers of the male and female mice showed an increased incidence of histopathological lesions (Table 7, below). Male mice showed a dose-related increase in both the incidence and severity of the histopathological lesions, 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, 14/20 showed minimal to mild hypertrophy, while 3/20 were classified as moderate.

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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 or higher. 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 ppm 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. In an effort to demonstrate that the vacuoles contained lipid, sections of male livers were stained using Oil Red O. No compound-related effect was found, since nearly all of the sections (including the controls) stained for microvesicular lipid.

2) Neoplastic: Not noted

D. DISCUSSION: Mice were exposed for 17 weeks to the test article incorporated in the diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively) for males and 0, 20, 500 or 2500 ppm (equivalent to 3.4, 85 or 434 mg/kg/day, respectively) for females. Males appeared to be more sensitive to the test article than females.

Significant increases in liver absolute and relative weight occurred in males dosed at ≥ 500 ppm, while in females significant increases were present only at 2500 ppm. Gross pathological examination of the livers from the male mice revealed a significant increase in enlargement and focal discoloration at ≥ 1450 and 2500 ppm, respectively. The female mice showed a significant increase in liver enlargement at 2500 ppm; focal discoloration was present at 2500 ppm, but was not significantly different from the control value. Significant clinical chemistry and histopathological were noted in both male and female mice. Males showed significant decreases in serum cholesterol at ≥ 1450 ppm after 13 weeks. Significant changes after 17 weeks included a decrease in serum cholesterol at ≥ 850 ppm and an increase in alanine aminotransferase at ≥ 1450 ppm. Mild to moderate hepatocellular hypertrophy and minimal to moderate necrosis and vacuolation occurred at ≥ 850 ppm, ≥ 1450 ppm and ≥ 2500 ppm, respectively, in the male mice. The severity of the lesions was dose-related with the more severe lesions occurring in the 1450 and 2500 ppm dose groups. However, the severity of the lesions was limited to mild to moderate.

12

Table 8: Incidence Data for Gross Pathological Lesions in the Liver

| Lesion | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| **Male** | | | | | | |
| Enlargement | 1/20 | 0/20 | 0/20 | 0/20 | 14/20* | 20/20* |
| Focal Discoloration | 0/20 | 0/20 | 0/20 | 2/20 | 5/20 | 6/20* |
| **Female** | | | | | | |
| Enlargement | 0/20 | 0/20 | 0/20 | --- | --- | 8/20* |
| Focal Discoloration | 0/20 | 0/20 | 0/20 | --- | --- | 3/20 |

* $p < 0.05$

Table 9: Incidence of Histopathological Lesions in the Liver

| Lesion | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| **Male** | | | | | | |
| Total Livers Examined | 20 | 20 | 20 | 20 | 20 | 20 |
| Hypertrophy | 0 | 0 | 4 | 14** | 20** | 20** |
| Necrosis | 1 | 0 | 2 | 4 | 8* | 12** |
| Individual Cell | 0 | 0 | 0 | 0 | 2 | 12** |
| Total Affected | 1 | 0 | 2 | 4 | 10** | 18** |
| Vacuolation | 0 | 0 | 6* | 2 | 3 | 10** |
| Individual Cell | 0 | 0 | 0 | 0 | 0 | 6** |
| Total Affected | 0 | 0 | 6* | 2 | 3 | 16** |
| **Female** | | | | | | |
| Total Livers Examined | 20 | 20 | 20 | 20 | 20 | 20 |
| Hypertrophy | 0 | 0 | 0 | --- | --- | 17** |
| Necrosis | 0 | 0 | 0 | --- | --- | 6* |
| Individual Cell | 0 | 0 | 0 | | | 1 |
| Total Affected | 0 | 0 | 0 | | | 6* |
| Vacuolation | 0 | 0 | 0 | --- | --- | 2 |
| Individual Cell | 0 | 0 | 0 | | | 1 |
| Total Affected | 0 | 0 | 0 | | | 3 |

* $p < 0.05$, ** $p < 0.01$

For the female mice, toxicity was only apparent at the 2500 ppm level. 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.

CONCLUSIONS: For 17 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively) for males and 0, 20, 500, or 2500 ppm (equivalent to 3.4, 85 or 434 mg/kg/day, respectively) for females.

| | NOEL | LOEL |
|---|---|---|
| Male | 20 ppm (LDT) | 500 ppm (MDT1) |
| Female | 20 ppm (LDT) | 2500 ppm (HDT) |

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

CASWELL FILE

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 13 Mar 92 009373
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D. E.A. Doyle 3/18/92
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 90-day oral - Mouse (82-1) TOX. CHEM. NO.: 323EE

MRID NO.: 420505-02

TEST MATERIAL: Propiconazole

SYNONYMS: CGA-64250

STUDY NUMBER: F-00107

SPONSOR: Ciba-Geigy Corp., Agricultural Division
P.O. Box 18300, Greensboro, NC 27419

TESTING FACILITY: Ciba-Geigy Corp., Environmental Health Center
400 Farmington Avenue, Farmington, CN 06032

TITLE OF REPORT: 13-Week Toxicity Study with CGA 64250 in Male Mice

AUTHOR: Robert F. Potrepka and John C. Turnier

REPORT ISSUED: April 30, 1991

CONCLUSIONS: For 13 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively).

NOEL = 20 ppm (LDT)

LOEL = 500 ppm (MDT1)

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

(Note: The study as submitted is flawed in that the interim and terminal sacrifice data were combined. The pathology incidence data for the 4, 8 and 13 week time points were obtained (via FAX) from the sponsor at the request of the primary reviewer and are appended to this report.)

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

A. MATERIALS:

1. Test compound: Propiconazole Description: yellow viscous liquid, Batch #: FL-850083, Purity: 92.0%, Contaminants: List in CBI appendix

2. Test animals Species: Mouse (male) Strain: Crl:CD-1 (ICR) BR (Swiss) Age: 37 days Weight (g): 21.4 - 31.2, Source: Charles River Laboratories, Inc., Raleigh, NC.

B. STUDY DESIGN:

1. Animal assignment: Male mice were assigned randomly to three test groups (Table 1, below). The first two groups were scheduled for interim sacrifice after 4 and 8 weeks, while the third group was sacrificed at the termination of the study.

| Test Group | Dose in Diet (ppm) | Animals/Group at Week | | |
|---|---|---|---|---|
| | | 4 | 8 | 13 |
| Control (CON) | 0 | 10 | 10 | 20 |
| Low (LDT) | 20 | 10 | 10 | 20 |
| Mid 1 (MDT1) | 500 | 10 | 10 | 20 |
| Mid 2 (MDT2) | 850 | 10 | 10 | 20 |
| Mid 3 (MDT3) | 1450 | 10 | 10 | 20 |
| High (HDT) | 2500 | 10 | 10 | 20 |

2. Diet preparation: The homogeneity and concentration of test article in the test diet mixture was measured after the first blend and monthly thereafter. Six samples of each dose level were analyzed and found to be within the acceptable limits. The concentration of test article at each dose level was analyzed and found to be within the acceptable range (86 to 101% of nominal).

3. Animals received food (Purina Certified Rodent Chow #5002) and water ad libitum.

4. Statistics: Statistical analyses consisted of an initial analysis of variance (ANOVA) followed by the Dunnett's test, if the outcome of the ANOVA was significant. The body weights and cumulative body weights were first analyzed using the Bartlett's test, and if a significance was found, ANOVA and Dunnett's Test were carried out. Trend analyses of the body weights and cumulative body weights were carried out using the Terpstra-Jonckheere test. The incidence data for histopathology findings were analyzed using the Fisher's exact test with Bonferroni's correction for multiple comparisons to a single control level.

16

5. Quality assurance was documented by signed and dated GLP and quality assurance statements.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of toxicity, moribundity and mortality.

a. Toxicity: There were no clinical observations attributable to the administration of the test article.

b. Mortality (survival): There were no unscheduled deaths during the study.

2. Body weight: Animals were weighed weekly during the 13 week treatment period.

a. Body Weight Data: Significant differences 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 (Table 1). A significant difference was also observed in the 1450 ppm group after 4 weeks.

b. Cumulative Body Weight Gain: The cumulative body weight gains showed significant decreases for animals in the 2500 ppm group during weeks 1, 2, and 4 (Table 1).

Table 1: Mean Animal Body Weights (g) and Cumulative Body Weight Gains

| Week of Study | Body Weight (g) | | Weight Gain (g) | |
|---|---|---|---|---|
| | 0 ppm | 2500 ppm | 0 ppm | 2500 ppm |
| 1 | 29.7 | 27.6** | 2.2 | 0.8** |
| 2 | 31.2 | 29.5** | 3.7 | 2.6** |
| 3 | 32.4 | 31.0* | 4.9 | 4.1 |
| 4 | 33.6 | 31.2** | 6.1 | 4.3** |
| 5 | 34.1 | 32.5** | 6.6 | 5.7 |
| 6 | 34.7 | 33.0** | 7.2 | 6.2 |
| 7 | 35.7 | 33.8** | 8.2 | 7.0 |
| 8 | 35.7 | 33.8* | 8.2 | 7.3 |

* $p < 0.05$, ** $p < 0.01$

3. Food consumption and compound intake: Food consumption was determined weekly and mean daily consumption was calculated.

a. Food consumption results: Significant findings for daily food consumption (g/animal/day) are summarized in Table 2, below.

Table 2: Daily Food Consumption (g/animal/day)

| Week of Study | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| 1 | 4.9 | 4.9 | 4.9 | 4.6* | 4.4** | 3.9** |
| 2 | 4.8 | 4.7 | 5.3* | 4.8 | 4.6 | 4.7 |
| 5 | 5.0 | 5.0 | 5.0 | 4.9 | 4.6* | 5.3* |
| 12 | 4.6 | 5.0 | 5.1* | 5.1* | 4.8 | 4.9 |

* $p < 0.05$, ** $p < 0.01$

b. Food Efficiency: Significant findings are summarized in Table 3, below.

Table 3: Food Efficiency (percent) (g body weight gain/g food consumed)

| Week of Study | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| 1 | 6.6 | 6.4 | 6.9 | 5.9 | 8.3 | 2.3** |
| 3 | 3.3 | 2.1* | 2.6 | 4.7** | 3.9 | 4.9** |
| 4 | 4.0 | 3.7 | 2.8 | 3.0 | 0.3** | 0.9** |
| 5 | 1.1 | 2.9** | 2.5* | 2.3* | 3.2** | 3.4** |
| 7 | 2.2 | 4.1** | 3.3 | 2.2 | 4.5** | 2.4 |
| 8 | 0.0 | 1.0 | 2.2** | 2.3** | 0.3** | 0.7 |
| 9 | 1.5 | 1.7 | -0.1* | 0.3 | 1.3 | 1.9 |
| 10 | 2.5 | 2.2 | 2.9 | 1.4 | 1.6 | 0.9* |
| 12 | 1.4 | 1.2 | 1.8 | 1.2 | 1.8 | -0.7** |

* $p < 0.05$, ** $p < 0.01$

c. Compound intake results: The average daily compound consumption is summarized below in Table 4.

Table 4: Average daily consumption of compound (mg/kg/day) at each dose level.

| Dose Level (ppm) | Compound Consumption |
|---|---|
| 20 | 2.7 |
| 500 | 65 |
| 850 | 112 |
| 1450 | 194 |
| 2500 | 352 |

4. Ophthalmological examinations: Examinations were performed on all animals at the termination of the study. No treatment-related eye lesions were observed.

5. Hematology and Clinical Chemistry: Clinical chemistry analyses were performed after 4 and 8 weeks of exposure and at the termination of the study (13 weeks). The checked (X) parameters were examined.

a. Hematology: Not performed

b. Clinical Chemistry

Electrolytes
- Calcium
- Chloride
- Magnesium
- Phosphorous
- Potassium
- Sodium

Enzymes
- X Alkaline phosphatase
- Cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- X Serum alanine aminotransferase (SGPT, ALT)
- X Serum aspartate aminotransferase (SGOT, AST)
- X Sorbitol Dehydrogenase

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- X Cholesterol
- Globulins
- Glucose
- Total Bilirubin
- Triglycerides
- Total Protein

Results: Significant clinical chemistry findings are shown in Table 5, below.

Table 5: Clinical Chemistry Findings

| Parameter (units) | Week of Study | Dose Level (ppm) 0 | 850 | 1450 | 2500 |
|---|---|---|---|---|---|
| Cholesterol (mg/dl) | 4 | 129 | 92** | 81** | 47** |
| | 8 | 114 | 104 | 58** | 57** |
| | 13 | 122 | 86** | 75** | 67** |
| Alanine Amino transferase (U/l) | 4 | 24 | 42 | 56** | 86** |
| | 8 | 24 | 30 | 53** | 74** |
| | 13 | 22 | 35 | 53** | 79** |
| Sorbitol Dehydrogenase (U/l) | 4 | 26 | 45* | 58** | 66** |
| | 8 | 27 | 30 | 47** | 59** |
| | 13 | 22 | 31* | 45** | 58** |

** $p<0.01$

6. Urinalysis: Not performed

7. Sacrifice and Pathology: Detailed pathological examination was performed on all animals in the control and treatment groups. The checked (X) tissues were collected for histological examination; the checked (XX) organs were also weighed.

| | | |
|---|---|---|
| Digestive system | Cardiovas./Hematol | Neurologic |
| Tongue | X Aorta | XX Brain |
| X Salivary glands | X Heart | X Periph. nerve |
| X Esophagus | X Bone marrow | X Spinal cord (3x) |
| X Stomach | X Lymph nodes | X Pituitary |
| X Duodenum | X Spleen | X Eyes (optic nerve) |
| X Jejunum | X Thymus | Glandular |
| X Ileum | Urogenital | X Adrenals |
| X Cecum | X Kidneys | Lacrimal gland |
| X Colon | X Urinary bladder | Mammary gland |
| X Rectum | X Testes | X Parathyroids |
| XX Liver | X Epididymides | X Thyroids |
| X Gall bladder | X Prostate | Other |
| X Pancreas | X Seminal vesicle | X Bone |
| Respiratory | Ovaries | X Skeletal muscle |
| X Trachea | Uterus | X Skin |
| X Lung | Vagina | X Joint |
| X Nasal Passages | Cervix | X Harderian glands |
| | | X Gross lesions |

a. Organ weights: At the end of the treatment period, the absolute and relative liver weights were determined. Table 6, below, summarizes the data.

Table 6: Absolute and relative liver weights

| Dose Level (ppm) | Absolute (g) | % of Body Weight | % of Brain Weight |
|---|---|---|---|
| 0 | 1.307 | 4.524 | 266.7 |
| 20 | 1.194 | 4.335 | 251.1 |
| 500 | 1.523* | 5.339** | 317.8 |
| 850 | 1.709** | 6.078** | 356.5** |
| 1450 | 1.984** | 7.043** | 414.5** |
| 2500 | 2.382** | 8.776** | 512.0** |

* $p < 0.05$, ** $p < 0.01$

b. Gross pathology: The only observations of toxicological significance were generalized enlargement and focal discoloration of the livers. The incidence data is presented in Table 7, below (See appended supplementary data).

Table 7: Incidence Data for Gross Pathological Observations in the Liver

| Observation | Week of Study | Animals per Group | Dose Level (ppm) | | | |
|---|---|---|---|---|---|---|
| | | | 0 | 850 | 1450 | 2500 |
| Enlargement | 4 | 10 | 0 | 1 | 3 | 10** |
| | 8 | 10 | 0 | 6* | 10** | 10** |
| | 13 | 20 | 0 | 7* | 19** | 20** |
| Prominent | 4 | 10 | 0 | 0 | 0 | 1 |
| Lobular | 8 | 10 | 0 | 0 | 1 | 5 |
| Architech. | 13 | 20 | 0 | 0 | 5 | 12** |

* $p < 0.05$, ** $p < 0.01$

c. Microscopic pathology

1) Non-neoplastic: Examination of the livers showed an increased incidence of histopathological findings are summarized in Table 8, below (See appended supplementary data). A dose-related increase in both the incidence and severity of hypertrophy, necrosis and vacuolation. Hypertrophy was mild to moderate with the more severe lesions occurring in the 1450 and 2500 ppm dose groups. Necrosis and vacuolation graded from minimal to moderate, and again, the

severity was dose-related. None of the lesions were classified as either marked or severe.

Table 8: Incidence of Histopathological Lesions in the Liver

| Lesion | Dose Level (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 20 | 500 | 850 | 1450 | 2500 |
| **Interval Period: 4 Weeks** | | | | | | |
| Total Livers Examined | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy | 0 | 0 | 2 | 6** | 10** | 10** |
| Necrosis | 1 | 0 | 0 | 4 | 3 | 6 |
| Individual Cell | 0 | 0 | 1 | 0 | 5* | 4 |
| Total Affected | 1 | 0 | 0 | 4 | 7* | 7* |
| Vacuolation | 0 | 0 | 0 | 0 | 1 | 6** |
| Individual Cell | 0 | 0 | 0 | 0 | 1 | 2 |
| Total Affected | 0 | 0 | 0 | 0 | 2 | 8** |
| **Interval Period: 8 weeks** | | | | | | |
| Total Livers Examined | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy | 0 | 0 | 5* | 9** | 10** | 10** |
| Necrosis | 0 | 0 | 2 | 2 | 4 | 6** |
| Individual Cell | 0 | 0 | 0 | 0 | 8** | 9** |
| Total Affected | 0 | 0 | 2 | 2 | 9** | 9** |
| Vacuolation | 0 | 0 | 1 | 0 | 4 | 4 |
| Individual Cell | 0 | 0 | 0 | 0 | 0 | 7 |
| Total Affected | 0 | 0 | 1 | 0 | 4 | 7** |
| **Interval Period: 13 weeks** | | | | | | |
| Total Livers Examined | 20 | 20 | 20 | 20 | 20 | 20 |
| Hypertrophy | 0 | 0 | 3 | 20** | 20** | 20** |
| Necrosis | 0 | 0 | 1 | 2 | 9** | 5* |
| Individual Cell | 0 | 0 | 0 | 1 | 10** | 16** |
| Total Affected | 0 | 0 | 1 | 3 | 15** | 18** |
| Vacuolation | 0 | 1 | 1 | 5* | 6* | 6* |
| Individual Cell | 0 | 0 | 0 | 0 | 3 | 18 |
| Total Affected | 0 | 1 | 1 | 5* | 9** | 6** |
| Mineralization | 0 | 0 | 0 | 2 | 0 | 6* |

* $p < 0.05$, ** $p < 0.01$

2) Neoplastic: Not noted

D. DISCUSSION: The objective of this study was to determine the MTD for the subchronic (13 week) administration of the test article to male mice. The test article was incorporated in the diet at 0, 20, 500, 850, 1450 or 2500 ppm. Significant increases in the absolute and relative liver weights at 500 ppm or higher correlated with gross pathological changes, histopathological changes and altered clinical chemistry findings. Hepatocellular hypertrophy, necrosis and vacuolation were significantly increased at 850 ppm, 1450 ppm and 2500 ppm, respectively. 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, however, were characterized as either marked or severe. Serum cholesterol was decreased at 850 ppm or higher and serum alanine aminotransferase was increased at 1450 ppm or higher.

CONCLUSIONS: For 13 weeks Crl mice were given the test material incorporated in diet at 0, 20, 500, 850, 1450 or 2500 ppm (equivalent to 2.7, 65, 112, 194 or 352 mg/kg/day, respectively).

NOEL = 20 ppm (LDT)

LOEL = 500 ppm (MDT1)

LOEL based on increase in absolute and relative liver weights.

Data do not support the assignment of an MTD to any of the doses tested in this study, since the severity of the histopathological lesions was not severe enough. Hematology was not performed. Clinical chemistry data is incomplete.

Classification: core - Supplementary

(Note: The study as submitted is flawed in that the interim and terminal pathology data were combined. The pathology incidence data for the 4, 8 and 13 week time points were obtained (via FAX) from the sponsor at the request of the primary reviewer and are appended to this report.)

This study does not satisfy guideline requirements (82-1) for a 90-day feeding study in mice.

RIN 1067-98

Propiconazole (Tilt) Tox Review

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