5-1-92

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tebuconazole (HWG 1608): The Strength of the Evidence Evaluation of Potential Developmental and Reproductive Toxicity From Exposure to Tebuconazole.

FROM: Alberto Protzel, Ph.D. 4/30/92
Toxicology Branch II
Health Effects Division (H7509C)

TO: Gary J. Burin, Ph.D., D.A.B.T.
Executive Secretary, HED Developmental and Reproductive Toxicity Peer Review.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: James N. Rowe, PH.D. James N. Rowe 5/1/92
Head, Section III
Toxicology Branch II
Health Effects Division

and

Marcia van Gemert, Ph.D.
Chief, Toxicology Branch II Marcia van Gemert 5/1/92
Health Effects Division

The attached package on Tebuconazole was prepared for consideration of the HED Peer Review Committee for Developmental and Reproductive Effects. The data for consideration are provided in summaries with Tables for each study, followed by copies of the DERs (Appendix) for each of the studies summarized. Please consider the issues listed on the following page:

## Issues and Questions for the Committee

1. The Committee is requested to comment on the significance, if any, of the developmental effects that occur in the three species at maternally toxic oral doses following in-utero exposure to tebuconazole.

2. What is the developmental toxicity potential of tebuconazole following dermal exposure, based on the results in mice and rats?

3. Will an additional risk assessment be required since an unacceptable MOE was determined for field workers using:

   - The NOEL obtained from a mouse oral developmental toxicity study.
   - Dermal penetration studies in rats using ethanol as a dosing vehicle.

4. Will additional data be required to assess the developmental toxicity potential of tebuconazole (e.g., bioavailability following dermal dosing in rats and mice).

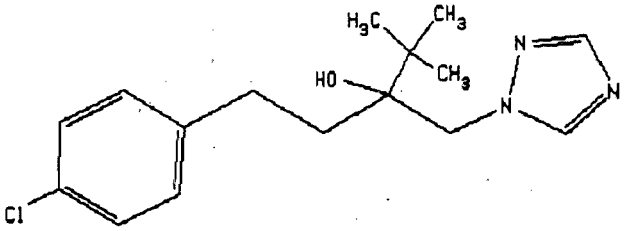
Table of Contents

Peer review for Tebuconazole.

## I. INTRODUCTION

Tebuconazole [α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol] is systemic fungicide used for cereals, peanuts, oilseed rape, grapes, bananas, stonefruit, and pome fruit. The Caswell No. is 463P and the CAS Registry No. is 107534-96-3. The producer of tebuconazole is Miles Inc. Kansas City, MO. Tebuconazole Technical is a crystalline material of 95-98.3% purity. The compound has a high octanol/water partition coefficient (≈ 5000, MRID 410685-04) and is soluble in organic solvents (e.g. ethanol).

The structure of tebuconazole is presented below:




## II. QUALITATIVE ASSESSMENT OF RELEVANT DATA

### A. Developmental Studies

1. Mice (Oral Dosing) -

References: HWG 1608, Study of Embryotoxic Effects on Mice After Oral Administration. M. Renhof. March 14, 1988. BAYER AG, Fachbereich Toxicologie, Institute of Toxicology/Agriculture, Wuppertal 1, FRG. MRID 408215-01. HWG 1608. This study was accompanied by: Supplementary Study of Maternal Toxicity to Mice After Oral Administration. M. Renhof and E. Karbe. March 9, 1988. BAYER AG, Fachbereich Toxicologie, Institute of Toxicology/Agriculture, Wuppertal 1, FRG. MRID 408215-01. Core Classification: Minimum.

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant NMRI/ORIG Kisslegg pregnant mice on days 6 through 15 of gestation at levels of 0, 10, 30, 100 mg/kg/day. Dams were sacrificed on day 18 of gestation and gross macroscopic observation of all organs was performed. At C-section the number of implantations and the number of live and dead fetuses were determined; in addition the fetuses were sexed, weighed and examined for external malformations. Approximately 30% of the fetuses were examined for visceral malformation by the modified Wilson technique, and approximately 70% were stained for evaluation of skeletal malformations by the Dawson method.

a. Maternal Toxicity

No compound-related mortality, clinical signs or effects on body weight gains were reported during the dosing period or during the entire gestation period. However, a supplementary study was conducted to further assess the maternal toxicity of the compound. Tebuconazole in aqueous 0.5% Cremophor was administered by gavage to pregnant NMRI/ORIG Kisslegg mice on days 6 through 15 of gestation at levels of 0, 10, 20, 30, 100 mg/kg/day. This supplementary study revealed the following apparently compound related effects:

- Statistically significantly decreased hematocrit (at 30-100 mg/kg) and mean corpuscular volume (at 20-100 mg/kg).

- Increased hepatic triglycerides, pale lobular liver, and increased severity of hepatic vacuoles and lipidosis at 100 mg/kg.

Based on the above findings from the supplementary study, the maternal toxicity NOEL was set at 10 mg/kg/day. The limited number of animals tested in the supplementary study plus the presence in the various test groups of pregnant and non-pregnant mice makes these findings suggestive but not definitive.

Cesarean Section Observations:

As summarized in Table 1, there was a dose-dependent and statistically significant increase in the number of runts (fetuses weighing less than 1.3 g) at the MDT (0.91) and the HDT (1.20) compared to controls (0.21). There was also a small, but statistically significant, increase in placental weight at the HDT. Although not statistically significant, the number of resorptions/dam was somewhat elevated at the HDT.

Table 1. Selected Cesarean Section Observations [1].

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. animals assigned | 25 | 25 | 25 | 25 |
| No. animals mated/inseminated | 25 | 25 | 25 | 25 |
| Pregnancy rate (%) | 24 (96) | 23 (92) | 23 (92) | 20 (80) |
| Total implantations | 255 | 258 | 247 | 228 |
| Implantations/dam | 10.6 | 11.2 | 10.7 | 11.4 |
| Total live fetuses | 236 | 235 | 235 | 202 |
| Live fetuses/dam | 9.8 | 10.2 | 10.2 | 10.1 |
| Total resorptions | 19 | 23 | 12 | 27 |
| Early resorpts./dam | 0.08 | 0.30 | 0.04 | 0.00 |
| Late resorpts./dam | 0.71 | 0.70 | 0.48 | 1.25 |
| Resorptions/dam (s.d.) | 0.80(1.0) | 1.0(1.6) | 0.5(0.8) | 1.3(2.2) |
| Post implantation loss (%) | 7.4 | 8.9 | 4.9 | 11.4 |
| Mean fetal weight, g (s.d.) | 1.36(0.08) | 1.37(0.07) | 1.37(0.13) | 1.30(0.12) |
| Mean placental wt., g (s.d.) | 0.10(0.01) | 0.10(0.01) | 0.10(0.02) | 0.11(0.01)* |
| Total No. of runts | 5 | 4 | 21 | 24 |
| No. of runts/dam (s.d.) | 0.21(0.51) | 0.18(0.50) | 0.91*(1.7) | 1.20*(2.12) |

[1] Data extracted from pp. 27-32 of the Study Report.
* Significantly different from controls ($p<0.05$).

b. Developmental Toxicity

As summarized in Table 2, there was a statistically significant ($p\leq0.05$) increase in the number of malformed fetuses per litter at the HDT (0.65 at the HDT vs 0.04 in controls). There was an increase in the number of affected fetuses and affected litters. The malformations were primarily in the skull, brain and spinal column. There was an elevation in the number of fetuses/dam with rudimentary ossification centers of the cranium in the HDT (1/1 in controls vs 5/4 in the HDT).

This study defines a developmental NOEL of 10 mg/kg and a developmental LOEL of 30 mg/kg, based on statistically significant, dose-dependent increases in runts at 30 mg/kg (MDT) and 100 mg/kg (HDT).

Table 2. **Selected** External/Visceral Malformations in Mice[a].

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| External Visceral Malformations | | | | |
| Total fetuses (ltrs) exmd. | 236(24) | 234(23) | 234(23) | 202(20) |
| Total fetuses (ltrs) affectd. | 1(1) | 4(2) | 0(0) | 13(8) |
| Visceral exam: fetuses(ltr) | 68(24) | 73(23) | 68(23) | 60(20) |
| -Multiple: cleft face, palate, jaw; dysplasia of limbs; deformed spinal | 1(1) | - | - | - |
| -Skull: cleft palate, micrognathia, partial dysplasia parietal bone | - | 4(2) | - | 7(6) |
| -Brain/spinal column: brain ventricle enlarged, asymmetry vertebral bodies, dysplasia spinal column, abnormal flexion spinal column | - | - | - | 5(4) |
| -Fused ribs, floating ribs | - | 1(1) | - | 1(1) |
| -Tail: kinked, shortened | - | - | - | 1(1) |
| Malformed fetuses/litter | 0.04 | 0.17 | 0 | 0.65* |

[a] Data extracted from pp. 14, 27-32 (Tables 1-5) of the Study Report.
* = significantly different from controls ($p<0.05$).

Table 3. Skeletal examination in mice[a].

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. fetuses(ltrs) examined | 168(24) | 161(23) | 166(23) | 142(20) |
| Sternum [No.fetuses(ltrs)] | | | | |
| -Ossif. ctrs. missing; slightly cleft sternum | 1(1) | - | - | - |
| Cranium | | | | |
| -Rudimentary ossif. ctrs. | 1(1) | - | 2(2) | 5(4) |
| Hyoid bone | | | | |
| -Missing, separate ossif. ctr. | 1(1) | 1(1) | - | 2(2) |
| Spinal column | | | | |
| -Vertebral bodies | - | - | - | 1(1) |

[a] Data extracted from pp. 27-32 (Tables 1-5) and pp 41-44 of the Study Report.

2. Mice (Dermal Dosing) -

References: Embryotoxicity study (including teratogenicity) with HWG 1608 Technical in the mouse (Dermal application). H. Becker et al. July 16, 1990. BAYER AG, Institut fur Toxicologie Landwirtschaft; Wuppertal 1, FRG. MRID 420103-01. This study was accompanied by: 'Supplementary study to: Embryotoxicity study (including teratogenicity) with HWG 1608 Technical in the mouse (Dermal application).' H. Becker et al. Date of the report was unspecified (Date of the last necropsy was August 9, 1989). BAYER AG, Institut fur Toxicologie Landwirtschaft; Wuppertal 1, FRG. MRID 408215-01, the Supplementary study was imbedded in the main study. Core Classification: Minimum

Tebuconazole (Technical) in aqueous 4% CMC was administered dermally to pregnant NMRI/KFM/HAN mice on days 6-15 of gestation at nominal levels of 0, 100, 300 and 1000 mg/kg/day. The test material was applied to an area of shaved skin (approximately 10% of the body surface) for 6 hours/day, the suface was covered with an occlusive bandage during the period of application. Dams were sacrificed on day 18 of gestation and gross macroscopic observation of all organs was performed. At C-section the uteri and their contents were weighed to obtain corrected maternal bodyweight gains and were examined to determine the number of implantations. The fetuses were sexed, weighed and examined for external malformations. Approximately 50% of the fetuses were examined for visceral malformations by Wilson's slicing technique, and the rest were cleared in potassium hydroxide and stained with alizarin S for evaluation of skeletal malformations.

a. Maternal Toxicity

No compound-related mortality, clinical signs or effects on body weight gains were reported during the dosing period or during the entire gestation period. However, a supplementary study was conducted to further assess the maternal toxicity of the compound. Tebuconazole in aqueous 4% CMC was administered dermally to pregnant NMRI/KFM/HAN mice on days 6 through 15 of gestation at levels of 0, 100 (LDT), 300 (MDT), and 1000 (HDT) mg/kg/day, following the same protocol as the main study. This supplementary study revealed the following compound related effects on the liver as the target organ:

- o Liver microsomal enzyme activities (cytochrome P-450, N- and O- demethylase) were significantly ($p \leq 0.01$) elevated (37-100%) at the MDT and the HDT.

- o There was a dose-dependent increase in the incidence and severity of fatty changes (stainable lipid deposition) in liver. The stainable fatty areas were limited to single cells in control and LDT mice and became extended to the periportal areas at the MDT and HDT. The severity of periportal deposition increased in going from the MDT (grades 1-2) to the HDT (grades 1-3)

- o Dose-dependent increase in the activities of AST (GOT) and ALT (GPT) in plasma (up to 37% at the HDT); this increase reached statistical significance vs controls for ALT at the HDT.

Based on the above findings from the supplementary study the maternal toxicity LOEL was set at 300 mg/kg/day and the NOEL at 100 mg/kg/day.

Cesarean Section Observations

Pregnancy rates ranged from 76.4% in controls and the MDT to 90% in the HDT (Table. 4). No treatment related effects were reported for the total and average (i.e. per dam) number of corpora lutea, implantations, resorptions (early and late), mean number of dead and live fetuses, fetal weights, and sex ratio.

Table 4: Cesarean Section Observations for Dams with Live Fetuses (From pp. 25, 56-57, 58-61, 70-97 and pp. 99-102 of the Study Report).

| Parameter | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #Animals Assigned | 34 | 30 | 34 | 30 |
| #Animals Mated/Inseminated | 34 | 30 | 34 | 30 |
| Pregnancy Rate (%) | 26(76.4) | 25(83.3) | 26(76.4) | 27(90) |
| Dams with Live Fetuses | 25[1] | 25 | 24[2] | 25[3] |
| Maternal Wastage | | | | |
| #Died | 0 | 0 | 0 | 0 |
| #Died/pregnant | 0 | 0 | 0 | 0 |
| #Non pregnant | 8 | 5 | 8 | 3 |
| #Aborted | 0 | 0 | 0 | 0 |
| #Premature Delivery | 0 | 0 | 0 | 1 |
| Total Corpora Lutea | 359 | 386 | 381 | 342 |
| Corpora Lutea/Dam | 14.4 | 13.4 | 15.90 | 13.7 |
| Preimplantation Loss [Tot(%)] | 42(11.7) | 25(6.5) | 21(5.5) | 39(11.4) |
| Mean (per dam) | 1.7 | 1.0 | 0.9 | 1.6 |
| # Dams affected | 20 | 14 | 14 | 17 |
| Total Implantations | 317 | 361 | 360 | 303 |
| Implantations/Dam | 12.7 | 14.4 | 15.0 | 12.1 |
| Postimplantation Loss[Tot(%)] | 16(5.0) | 29(8.0) | 23(6.4) | 18(5.9) |
| Mean (per dam) | 0.6 | 1.2* | 1.0 | 0.7 |
| # Dams affected | 8 | 19** | 16* | 12 |
| Total Live Fetuses | 301 | 332 | 337 | 285 |
| Live Fetuses/Dam[4] | 12.04 | 13.3 | 14.0 | 11.4 |
| Total Resorptions | 16 | 29 | 23 | 18 |
| Early ("Embryonic") | 12 | 20 | 16 | 14 |
| No. Dams affected | 5 | 14** | 13** | 9 |
| Late ("Fetal") | 4 | 9 | 7 | 4 |
| No. Dams affected | 3 | 7 | 7 | 3 |
| Resorptions/Dam | 0.64 | 1.2 | 0.96 | 0.72 |
| Total Dead Fetuses | 0 | 0 | 0 | 0 |
| Dead Fetuses/Dam | 0 | 0 | 0 | 0 |
| Mean Fetal Weight (gm) | 1.2 | 1.2 | 1.1 | 1.2 |
| Sex Ratio (% Males/litter) | 51.2 | 50.0 | 55.2 | 51.9 |

[1] One female (No. 16) had two implantation sites only).
[2] Two females (Nos. 69 and 80), had 6 and 9 implantation sites only.
[3] One female (No. 108) had 2 embryonic resorptions only; another female (No. 102) delivered prematurely on day 17 of gestation and was necropsied.
[4] Counting only dams with live fetuses (e.g. 25 in controls).

b. Developmental Toxicity

As shown in Table 5, the incidence of palatoschisis in the HDT was 12/285 fetuses (4.2%) vs. 8/301 fetuses in controls (2.7%) and exencephaly was observed in 2/285 (0.7%) at the HDT vs. 1/301 (0.3%) in controls. Litter frequencies for palatoschisis (7/25, 28%) or exencephaly (1//25, 4%) were identical in the HDT and controls. As summarized in Table 5a., historical control data [1 study only, 5/87-7/87, with NMRI/HAN/ outbred SPF quality mice] indicate palatoschisis in 5/307 (1.6%) fetuses and 5/24 (20.8%) litters and exencephaly in 1/307 (0.3%) fetuses and 1/24 (4.2%) litters.

Table 5. External examinations in cesarean-delivered mouse pups[a].

| Observations | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups (litters) examined | 301(25) | 332(25) | 337(24) | 285(25) |
| # pups (litters) affected | 9(8) | 10(8) | 6(6) | 15(9) |
| Finding: pups(litters) | | | | |
| Palatoschisis | 8(7) | 8(6) | 4(4) | 12(7) |
| Tail cranial-bended | 1(1) | - | 1(1) | - |
| Exencephaly | 1(1) | 1(1) | - | 2(1) |
| Hind leg malposition: | | | | |
| Right leg | 1(1) | - | 1(1) | - |
| Left leg | - | 1(1) | 2(2) | 2(2) |

[a] Data from pp. 62-63 and pp. 78-97 of the Study Report.

Table 5a. Palatoschisis and Exencephaly in the HDT vs controls.

| Observations | Historical[a] Controls | | Concurrent Controls | | This Study HDT | |
|---|---|---|---|---|---|---|
| | Pups(%) | Litts.(%) | Pups(%) | Litts.(%) | Pups(%) | Litts.(%) |
| No. Examined | 307 | 24 | 301 | 25 | 285 | 25 |
| Finding: | | | | | | |
| Palatoschisis | 5(1.6) | 5(20.8) | 8(2.7) | 7(28) | 12(4.2) | 7(28) |
| Exencephaly | 1(0.3) | 1(4.2) | 1(0.3) | 1(4.0) | 2(0.7) | 1(4.0) |

[a] 1 study only, 5/87-7/87, with NMRI/HAN/ outbred SPF mice; from p 228 of the Study Report.

As shown in Table 6, examination of the skeletal findings revealed statistically significant increases in the fetal incidences of bipartite sternebra 5, supernumerary ribs, and non-ossification of phalanxes in the forelimbs, in addition to up to two-fold increases in their litter incidences:

- o Bipartite sternebra 5: fetuses: 11.0% (HDT) vs 3.8% (controls) [($p \leq 0.05$)] and litters: 40% (HDT) vs 20% (controls).
- o Supernumerary ribs, one, right: fetuses: 72% (HDT) vs 48% (controls) [($p \leq 0.01$)] and litters 100 % (HDT) vs 88% (controls).
- o Left forelimb, non-ossified distal phalanx digit 2: fetuses: 12.4% (HDT) vs 6.2% (controls) [($p \leq 0.05$)], and litters 44% (HDT) vs 32% (controls).
- o Right forelimb, non-ossified distal phalanx, digit 4: fetuses: 13% (HDT) vs 9.7% (controls) [($p \leq 0.05$)] and litters: 40% (HDT) vs 28% (controls).

Examination of Table 6 also indicates that, in addition, there were statistically significant decreases at the HDT and/or LDT in the fetal incidence of non-ossified phalanxes of the hindlimbs. These effect, however, did not produce any marked effects in litter incidences.

The above statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT.

This study defines a LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity in mice after dermal dosing.

Table 6. Summary of skeletal observations in cesarean-delivered mouse pups. Data from pp. 65-69 and 231-443 of the Study Report.

| Observations | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups (litters) examined | 159(25) | 171(25) | 175(24) | 145(25) |
| SKULL | | | | |
| Part of cranium missing, (externally, as exencephaly) | 1(1)[a] | - | - | - |
| CERVICAL VERTEBRAE | | | | |
| Vertebra 2 (Non-ossified) | 19(9) | 10*(6) | 20(8) | 14(8) |
| STERNUM | | | | |
| Assymetric sternebrae (2-5) or (4 and 5) | 3(3) | 1(1) | 1(1) | - |
| Assymetric and bipartite sternebrae (2-5) | - | - | - | 1(1) |
| Assymetric sternebra (3 and 4) | - | - | - | 1(1) |
| Incompletely ossified Sternebra 5 | 128(25) | 134(25) | 156*(24) | 108(24) |
| Bipartite sternebra 5 | 6(5) | 9(7) | 2(1) | 16*(10) |
| RIBS | | | | |
| Supernumerary "flying rib" (No. 14), left | - | - | 1(1) | - |
| Supernumerary, one, left | 92(23) | 106(25) | 105(22) | 107*(25) |
| Supernumerary, one, right | 76(22) | 100*(25) | 91(22) | 105**(25) |
| LEFT FORELIMB (Non-ossified) | | | | |
| Digit 2, medial phalanx | 139(25) | 149(25) | 150(24) | 122(23) |
| Digit 2, distal phalanx | 10(8) | 9(7) | 3*(3) | 18*(11) |
| Digit 4, distal phalanx | 10(8) | 9(6) | 3*(3) | 17(10) |
| RIGHT FORELIMB (Non-ossified) | | | | |
| Digit 2, medial phalanx | 137(25) | 143(25) | 145(24) | 122(23) |
| Digit 2, distal phalanx | 9(7) | 9(7) | 5(4) | 16(8) |
| Digit 4, distal phalanx | 9(7) | 11(7) | 5(4) | 19*(10) |
| LEFT HINDLIMB (Non-ossified) | | | | |
| Toe 5, proximal phalanx | 34(10) | 17**(9) | 29(11) | 14**(8) |
| Toe 5, distal phalanx | 32(10) | 16**(7) | 19*(9) | 25(13) |
| RIGHT HINDLIMB (Non-ossified) | | | | |
| Toe 5, proximal phalanx | 32(9) | 16*(9) | 31(13) | 15*(9) |
| Toe 5, distal phalanx | 30(10) | 15*(7) | 19(10) | 25(13) |

[a] Fetal(litter) incidence.
* Significant at the 5% level. ** Significant at the 1% level.

3. Rats (Oral) Range Finding Study -

Reference: Dose range-finding embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rat. H. Becker. June 1, 1987. BAYER AG, Institut fuer Toxicologie Landwirtschaft, Fachbereich Toxicologie, D-5600 Wuppertal, FRG. MRID 407009-42. Core Classification: Supplementary.

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant Wistar/HAN (Kfm, WIST, Outbred SPF quality) rats (5/dose level) on days 6-15 of gestation at levels of 0, 10, 30, and 90 mg/kg/day. Dams were sacrificed on day 21 of gestation and gross macroscopic observation of all organs was performed. At C-section the uteri and their contents were weighed to obtain corrected maternal bodyweight gains and were examined to determine the number of implantations.

The following observations were made:

- o Body weight gain in the HDT was somewhat less than in the controls during days 6-11 (8.1% in controls vs 4.9% HDT) and for days 6-16 of gestation (19.5% in controls vs 15.5% HDT) with a slight suggestion of rebound for days 16-21 of gestation.
- o Mean food consumption was -3.7% of controls at the HDT during treatment.
- o Embryonic and fetal resorptions (% of implantations) were approximately doubled in the HDT group vs controls (6.2% controls vs. 12.1% HDT). This was due to an increase in mean fetal resorptions (1.5% controls vs. 6.1% HDT).

Based on the above results doses for the main rat teratology study [see below, MRID 407009-43] were set at 0, 30, 60, and 120 mg/kg/day.

4. Rat (Oral) Main Study

Reference: Embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rat. H. Becker. April 28, 1988. BAYER AG, Institut fuer Toxicologie Landwirtschaft, Fachbereich Toxicologie, D-5600 Wuppertal, FRG. MRID 407009-43. Core Classification: Minimum

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant Wistar/HAN (Kfm, WIST, Outbred SPF quality) rats on days 6-15 of gestation at levels of 0, 30, 60 and 120 mg/kg/day. Dams were sacrificed on day 21 of gestation and gross macroscopic observation of all organs was performed. At C-section the uteri and their contents were weighed to obtain corrected maternal body weight gains and were examined to determine the number of implantations. The fetuses were sexed, weighed and examined for external malformations. Approximately 50% of the fetuses were examined for visceral malformations and brain anomalies by Wilson's slicing technique, and the rest were cleared in potassium hydroxide and stained with alizarin S for evaluation of skeletal malformations.

a. Maternal Toxicity

No compound related mortality or clinical signs of toxicity were reported at any dose level. Although body weight gains for days 6-21 of gestation were slightly decreased (85% of controls) at the HDT, corrected or uncorrected bodyweight gains were not significantly different from controls at any dose level. Mean daily food consumption during days 6-16 (which included the dosing period, days 6-15) was significantly decreased with respect to controls ($p<0.05$) at the MDT (-7%) and at the HDT (-15%). There was a slight increase in daily food consumption (about 5%) during the post-dosing period. A significant decrease ($p<0.05$) in absolute body weight was reported for the HDT and a dose-dependent and statistically significant increase ($p<0.01$) in liver weight/body weight was reported at the MDT and the HDT (Table 7). Based on the above findings the LOEL for maternal toxicity was set at 60 mg/kg/day (MDL) and the NOEL at 30 mg/kg/day.

Table 7. Body and liver weight and liver to body weight ratio in pregnant rats.

| Effect | Dose level | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| Body weight (g.; 21 d.; absol). | 320 | 314 | 322 | 303* |
| Liver weight (g) | 11.51 | 11.55 | 12.50 | 12.49* |
| Liver/body weight ratio | 3.59 | 3.68 | 3.89** | 4.12** |

* and ** indicate significant at the 0.05 and 0.01 level, respectively.

Cesarean Section Observations:

As summarized in Table 8, the following statistically significant ($p<0.05$) effects, with respect to controls, were reported at the HDT:

- Increase in the numbers of early and late resorptions.
- Decrease in mean fetal weights (-10.6%) and in total live fetuses (19.4% below controls). This latter value was reflected in the decreased number of live fetuses/dam (9.7 HDT vs 12.0 controls) and is consistent with the increased resorptions and % postimplantation loss observed at the HDT.

The mean fetal weight depression may be treatment-related since the decrease in mean fetal weight was observed despite a reduction in litter size in the HDT.

Table 8. Cesarean Section Observations in Rats[a]

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. animals assigned | 25 | 25 | 25 | 25 |
| No. animals mated/inseminated | 25 | 25 | 25 | 25 |
| Pregnancy rate(%) | 96 | 96 | 96 | 96 |
| Total corpora lutea | 357 | 347 | 314 | 370 |
| Corpora lutea/dam | 14.9 | 14.5 | 14.3 | 15.4 |
| Total implantations | 302 | 291 | 277 | 298 |
| Implantations/dam | 12.6 | 12.1 | 12.6 | 12.4 |
| Total live fetuses | 288 | 271 | 256 | 232* |
| Live fetuses/dam | 12.0 | 11.3 | 11.6 | 9.7 |
| Total resorptions | 14 | 20 | 21 | 66 |
| Early | 14 | 20 | 19 | 45* |
| Late | 0 | 0 | 2 | 21* |
| Resorptions/dam | 0.6 | 0.8 | 1.0 | 2.8 |
| Total dead fetuses | 0 | 0 | 0 | 0 |
| Total dead fetuses/dam | 0 | 0 | 0 | 0 |
| Mean fetal weight (g) | 4.7 | 4.7 | 4.6 | 4.2* |
| Preimplantation loss (%) | 15.4 | 16.1 | 11.8 | 19.5 |
| Postimplantation loss (%) | 4.6 | 6.9 | 7.9 | 22.1 |

[a] Data from pp 20, 28-29 of the Study Report (MRID 407009-43).
* = $p<0.05$.

b. Developmental Toxicity

External examination of fetuses (Table 9) revealed a missing tail in one HDT fetus, and agnathia (lower jaw), microstomia and anophthalmia in another fetus of a different HDT litter. Based on the absence of comparable findings in the controls, these findings may be compound-related malformations.

Historical control data for missing tail for 1985-1988 (Appendix 5) indicate a low frequency for this effect. As shown in Appendix 5, out of a total of 31 studies comprising 763 litters and 8822 fetuses, agenesis of tail has been observed only once in each of two studies [one study in 1987 and another in 1985]. The low overall litter frequency of this effect (2/763, 0.26%) suggests that, as observed in this study, the effect may be treatment-related.

The same set of historical control data indicates that anopthalmia and decreased or absent jaw development has been observed only once in each of two studies [one study in 1986 and another in 1985. The low overall litter frequency of this effect (2/763, 0.26%) suggests that, as observed in this study, the effect may be treatment-related.

Visceral examination of fetuses (Table 9) revealed findings of excess fluid in the thoracic cavity at the HDT (3 pups in 1 litter, 1 pup in another litter) and at the LDT (1 pup). The effect may be possibly considered to be compound related; it was not listed in the historical control data appearing in Appendix 5, comprising 31 studies [4191 viscerally examined fetuses, and 763 litters] over the years 1985-1988.

Table 9. External/Visceral Malformations in Rats. Data from MRID 407009-43.

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| External Examinations | | | | |
| No. pups (litters) exmd. | 288(24) | 271(24) | 256(22) | 232(24) |
| No. pups (litters) affectd. | 0 | 0 | 0 | 2(2) |
| Missing tail, % | 0 | 0 | 0 | 0.4(4.2)[a] |
| Agnathia (lower jaw), microstomia, anophthalmia, % | 0 | 0 | 0 | 0.4(4.2) |
| Visceral Examinations | | | | |
| No. pups (litters) exmd. | 144(24) | 134(24) | 129(24) | 116(24) |
| Excess fluid in thoracic cavity | 0 | 0.7(4.2) | 0 | 3.4(8.3) |
| Missing tail | 0 | 0 | 0 | 0.9(4.2) |
| Agnathia (lower jaw), microstomia, anophthalmia | 0 | 0 | 0 | 0.9(4.2) |

[a] Historical control incidence for "agenesis of the tail" for 1985-1988 was: 2/8822 fetuses and 2/763 litters (Appendix 5).

Skeletal examination revealed dose-dependent, statistically significant increases in several fetal frequencies and some litter frequencies of skeletal variations. As shown in Table 10, skeletal variations observed to have increased fetal frequencies in both the MDT and the HDT were nonossified cervical vertebra 2, vertebral arch 6 (right), digit 1 distal phalanx (left), digit 3 proximal phalanx (left and right), digit 2 proximal phalanx (right), digit 4 proximal phalanx (right) and toe 5 distal phalanx (right). Because the Study Report contained tabulation of only the fetal frequencies for the skeletal observations, the litter frequencies for some of the significantly elevated fetal frequencies were determined by the reviewer [using individual data in the Study Report] and are summarized in Table 11.

As summarized in Table 11:

- o There was a dose-dependent increase in the litter and fetal incidences of non-ossified sacral vertebral arch 6 (R), which is statistically significant vs controls at the MDT and the HDT [i.e. litter incidences: 2/24, 8.3% (LDT), 6/22, 27.2% (MDT) and 8/24, 33.3% (HDT) vs 0/24 controls]. Historical controls (Appendix 5) indicate that the effect is very infrequent: it was observed once in 1 of 31 studies (at a litter incidence of 4% for the study) at an overall litter incidence for the 31 studies of 1/763 (0.13%).

- o There was a dose-dependent increase in the fetal incidences of nonossification of the digit 4 proximal phalanxes (R) with statistically significant litter and fetal incidences at the MDT and HDT [i.e. litter incidences: 6/24, 25% (MDT and HDT) vs 1/24, 4% (controls)]. Historical controls (Appendix 5) indicate that litter frequencies for this effect are in the range of 4.2-47.8%.

- o Coupled to the marked increase in fetal incidence of non-ossification of cervical vertebra 2 (41.4% at the HDT vs 20.1% in controls) there is an increased litter incidence 20/24 (83.3%) at the HDT vs 14/24 (58.3%) in controls which does not quite reach statistical significance (p=0.055). It is noted, however that the historical control range (Appendix 5) for litter frequencies is 36-80%.

These effects on litter/fetal incidences appear to be consistent with a treatment-related developmental effect of tebuconazole at the MDT and HDT.

In addition, as shown in Table 10, the fetal and litter incidences of dumbell shaped centrum in thoracic vertebrae are increased at the HDT (5.1% fetuses, 16.6% litters) vs controls (1.4% fetuses, 8.3% litters). These values, although not statistically significantly different from concurrent controls, exceed values for historical controls for 1988, 1986 and 1985 (0-13.6%, Appendix 5). Values for 1987 should not be included since they include other related effects.

There was also an increase in the litter incidence of supernumerary ribs at the MDT and the HDT [13/22 (55%) litters at the MDT and 12/24 (50%) at the HDT vs 9/24 (37.5%) in controls] coupled to statistically significant increases in their fetal incidence at the HDT. These litter incidences for supernumerary ribs, however, are within historical control ranges illustrated in Appendix 5 for 1987-

1988, which showed litter incidences of up to 56.0-70.8% for supernumerary ribs.

Thus, this study defines a LOEL for developmental effects of 60 mg/kg/day (MDT) and a developmental NOEL of 30 mg/kg/day.

Table 10. Skeletal Observations in Rat Fetuses. Data from MRID 407009-43.

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. pups (litters) exmd. | 144(24) | 137(24) | 127(22) | 116(24) |
| Thoracic Vertebrae | | | | |
| Centrum dumbbell shaped (10-13th) | 2(2)[a] | 2(2) | 2(2) | 6(4) |
| Centrum bipartite (10-12th) | 0 | 0 | 0 | 4(2) |
| Cervical Vertebra (Nonossified) | | | | |
| Total litters affected | 18 | 19 | 18 | 23 |
| Number of fetuses(% incidence): | | | | |
| Cervical vertebra 1 | 18(3) | 21(15) | 24(19) | 48(41)** |
| Cervical vertebra 2 | 29(20) | 40(29) | 38(30)* | 48(41)** |
| Cervical vertebra 3 | 9(6) | 10(7) | 12(9) | 16(14)* |
| Cervical vertebra 4 | 0 | 5(4) | 2(2) | 13(11)** |
| Cervical vertebra 5 | 3(2) | 3(2) | 3(2) | 10(9)* |
| Cervical vertebra 6 | 1(1) | 2(1) | 2(2) | 6(5)* |
| Sacral Vertebrae (Nonossified) | | | | |
| Total litters affected | 18 | 18 | 15 | 21 |
| Number of fetuses(% incidence): | | | | |
| Vertebral arch 6, left | 1(1) | 2(1) | 3(2) | 14(12)** |
| Vertebral arch 6, right | 0 | 2(1) | 6(5)** | 13(11)** |
| Vertebral arch 7, left | 50(35) | 53(39) | 49(39) | 66(57)** |
| Vertebral arch 7, right | 45(31) | 53(39) | 51(40) | 65(56)** |
| Sternum (Incompletely ossified) | | | | |
| Total litters affected | 18 | 15 | 15 | 19 |
| Number of fetuses(%incidence): | | | | |
| Sternebra 2 | 4(3) | 3(2) | 3(2) | 15(13)** |
| Sternebra 6 | 0 | 0 | 1(1) | 4(3)* |
| Supernumerary ribs (one, L or R) | | | | |
| Total litters affected | 9 | 11 | 13 | 12 |
| Number of fetuses (%incidence): | | | | |
| Ribs, left | 14(10) | 20(15) | 18(14) | 26(22)** |
| Ribs, right | 15(10) | 23(17) | 19(15) | 24(21)* |

[a] * = ($p<0.05$); ** = ($p<0.01$). (Continued)

Table 10. Skeletal Observations (Continued from previous page).

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. pups (litters) exmd. | 144(24) | 137(24) | 127(22) | 116(24) |
| Forelimbs, Left or Right (Nonossified) | | | | |
| Total litters affected | 23 | 20 | 20 | 19 |
| Number of fetuses(% incidence): | | | | |
| Digit 2 proximal phalanx (l) | 27(19) | 36(26) | 37(29)* [a] | 42(36)** |
| Digit 3 proximal phalanx (l) | 0 | 3(2) | 5(4)* | 9(8)** |
| Digit 4 proximal phalanx (l) | 2(1) | 7(5) | 7(6) | 11(9)** |
| Metacarpal 5 (l) | 0 | 0 | 2(2) | 4(3)* |
| Digit 5 distal phalanx (l) | 55(38) | 56(41) | 55(43) | 23(20)** |
| Digit 2 proximal phalanx (r) | 27(19) | 33(24) | 39(31)* | 40(34)** |
| Digit 3 proximal phalanx (r) | 0 | 3(2) | 4(3)* | 8(7)** |
| Digit 4 proximal phalanx (r) | 1(1) | 6(4) | 6(5)* | 11(9)** |
| Metacarpal 5 (r) | 0 | 0 | 2(2) | 5(4)* |
| Digit 5 distal phalanx (r) | 45(31) | 56(41) | 47(37) | 21(18)* |
| Hind Limb, Left or Right (Nonossified) | | | | |
| Total litters affected | 24 | 24 | 22 | 24 |
| Number of fetuses(% incidence): | | | | |
| Metatarsal 1 (l) | 18(13) | 24(18) | 18(14) | 31(27)** |
| Toe 2 proximal phalanx (l) | 107(74) | 92(67) | 96(76) | 103(89)** |
| Toe 3 proximal phalanx (l) | 81(56) | 70(51) | 78(61) | 87(75)** |
| Toe 4 proximal phalanx (l) | 79(55) | 65(47) | 72(57) | 85(73)** |
| Toe 5 distal phalanx (l) | 1(1) | 9(7)** | 5(4) | 7(6)* |
| Metatarsal 1 (r) | 18(13) | 24(18) | 20(16) | 32(28)** |
| Toe 2 proximal phalanx (r) | 110(76) | 96(70) | 105(83) | 105(91)** |
| Toe 3 proximal phalanx (r) | 86(60) | 75(55) | 76(60) | 92(79)** |
| Toe 4 proximal phalanx (r) | 81(56) | 71(52) | 74(58) | 91(78)** |
| Toe 5 distal phalanx (r) | 1(1) | 9(7)** | 6(5)* | 7(6)* |

[a] * = ($p<0.05$); ** = ($p<0.01$).

Table 11. Selected Skeletal Observations[a,b]. Data from MRID 407009-43.

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. pups (litters) examined | 144(24) | 137(24) | 127(22) | 116(24) |
| Vertebrae (Nonossified) | | | | |
| No. pups (litters): | | | | |
| Cervical vertebra 2 | 29(14) | 40(17) | 38*[c](17) | 48**(20)[d] |
| Sacral vertebral arch 6 (R) | 0(0) | 2(2) | 6*(6)** | 13**(8)** |
| Forelimbs (Nonossified) | | | | |
| No. pups (litters): | | | | |
| Digit 2 proximal phalanx (L) | 27(14) | 36(14) | 37*(16) | 42**(18) |
| Digit 3 proximal phalanx (L) | 0(0) | 3(3) | 5*(5)* | 9**(4) |
| Digit 3 proximal phalanx (R) | 0(0) | 3(3) | 4*(4) | 8**(4) |
| Digit 4 proximal phalanx (R) | 1(1) | 6(4) | 6*(6)* | 11**(6)* |
| No. pups (litters): | | | | |
| Toe 5 distal phalanx (L) | 1(1) | 9**(6) | 5(5) | 7*(3) |
| Toe 5 distal phalanx (R) | 1(1) | 9**(6)* | 6*(6)* | 7*(3) |

[a] Entries for this table were selected from Table 10 for litter incidence tabulation on the basis of their fetal incidences being significantly different from controls at the HDT and at a lower dose (MDT or LDT or both).
[b] Fetal incidences were tabulated by the Study Authors. Litter incidences were tabulated by the reviewer using individual data in the Study Report.
[c] Fisher's exact test was used by the Study Authors to analyze fetal data and by the EPA reviewer to analyze litter data. * if $p \leq 0.05$, ** if $p \leq 0.01$
[d] $p=0.055$

5. Rat (Dermal Dosing) -

Reference: Study for embryotoxic effects on rats after dermal administration. M. Renhof. August 30, 1988. Mobay Corporation (Sponsor). Bayer AG. Institiute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany (Testing Facility). MRID 414508-01. Core Classification: Supplementary.

Tebuconazole (Technical) in aqueous 1% Cremophor EL was administered dermally to pregnant Bor:WISW (SPF Cpb) rats on days 6-15 of gestation at nominal levels of 0, 100, 300 and 1000 mg/kg/day. The test material was applied to a 25 $cm^2$ area of shaved skin (approx. a nominal dose of 0, 0.87, 2.6, and 8.7 $mg/cm^2$/day) for 6 hours, then removed followed by washing of the application site with lukewarm water. Dams were sacrificed on day 20 of gestation and gross macroscopic observation of all organs was performed. At C-section the uteri and their contents were weighed to obtain corrected maternal bodyweight gains and were examined to determine the number of implantations. The fetuses were sexed, weighed and examined for external malformations. Approximately 50% of the

fetuses were examined for visceral malformations by Wilson's technique, and the rest were cleared in potassium hydroxide and stained with alizarin S for evaluation of skeletal malformations by Dawson's method.

No evidence of maternal toxicity (changes in body weights, corrected body weights, food consumption, clinical signs, pathology, deaths, abortions, premature deliveries) were noted at any dose level.

No developmental toxicity was noted at any dose level based upon indices of mean corpora lutea/dam, implantations/dam, live or dead fetuses/dam, resorptions/dam (early and late), mean fetal weights, sex ratios (% male), mean crown-rump length (cm), mean runts/dam, variations or malformations.

The adequacy of this study (classified supplementary) remains to be determined since it is unclear whether the dermal application of tebuconazole in aqueous suspension resulted in sufficient exposure to the test compound. Although dermal absorption of tebuconazole in ethanol has been reported for rats (See Section III C of this document), the extent of dermal absorption of tebuconazole from aqueous suspension is not known.

6. Rabbit (Oral) Range Finding Study -

Reference: Dose range-finding embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rabbit. H. Becker (Study director). February 4 1987. BAYER AG (Sponsor). RCC, research & Consulting Company AG and RCC, Umweltchemie AG, CH 4452 Itingen/Switzerland (Testing Facility). MRID 407009-44. Core Classification: Supplementary.

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant Chinchilla rabbits (Kfm: CHIN hybrids) on days 6-18 of gestation at levels of 0, 30, 100 and 300 mg/kg/day. Dams were sacrificed on day 28 of gestation for gross macroscopic observation of organs and removal of fetuses.

The following observations were made:

- Reduced body weight gains during the treatment period were observed at the HDT [+210 g (controls) vs -157 g (HDT)].
- Decreased food consumption during treatment at the HDT (-12.1% of controls).
- At the HDT, the single pregnant doe (out of 3) had 100% implantation losses.
- Live fetuses/dam increased in dose-dependent fashion: Control: 7.0; LDT: 7.3; MDT: 5.3; and HDT: 0.

Based on these observations, the doses for the Main study were set at 0, 10, 30, and 100 mg/kg/day.

7. Rabbit (Oral) Main Study

Reference: Embryotoxicity (including teratogenicity) study with HWG 1608 TECHNICAL in the rabbit. H. Becker (Study director). February 26 1987. BAYER AG (Sponsor). RCC, Research & Consulting Company AG and RCC, Umweltchemie AG, CH 4452 Itingen/Switzerland (Testing Facility). MRID 407009-45. Core Classification: Minimum.

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant Chinchilla rabbits (Kfm: CHIN hybrids) on days 6-18 of gestation at levels of 0, 10, 30, and 100 mg/kg/day. Dams were sacrificed on day 28 of gestation and gross macroscopic observation of all organs was performed. At C-section the uteri and their contents were weighed to obtain corrected maternal body weight gains and were examined to determine the number of implantations. The fetuses were sexed, weighed and examined for external malformations. Fetal body cavities and organs were examined. Crania of all fetuses were examined for ossification. Heads were fixed in trichloroacetic acid and formaldehyde and serially sectioned and examined. Trunks were cleared in potassium hydroxide and stained with alizarin red S for skeletal examination.

a. Maternal Toxicity

No compound related mortality or clinical signs of toxicity were reported at any dose level. Mean body weight gains during dosing were slightly lower in the HDT (+6.1%) than in controls (+10.6%); this weight loss was associated with a decrease in food consumption during dosing (-12.1% of controls) and with a rebound during days 24-28 of gestation (+32.8%). Likewise, corrected body weight gains for days 6-28 of gestation were slightly smaller in the HDT (-0.3%) than in controls (1.4%). Statistical analysis by the author indicated significantly reduced body weight gains between days 7 to 25 of gestation. Based on the above findings the NOEL for maternal toxicity was set at 30 mg/kg/day and the LOEL was set at 100 mg/kg/day.

Cesarean Section Observations:

A statistically significant ($p < 0.05$) increase in fetal resorptions was observed at the HDT (Table 12). This increase in fetal resorptions was reflected in the somewhat decreased number of live fetuses per dam in the HDT (6.4 vs 7.4 in controls). The incidence of post-implantation loss at the HDT (27.4%) was significantly increased ($p \leq 0.05$) vs controls (8.3%). The number of early resorptions in the HDT, although apparently increased with respect to controls was not significantly increased ($p = 0.064$).

b. Developmental Toxicity

External examination of fetuses revealed the presence of frank malformations in the HDT only. These malformations included peromelia in 5 fetuses (4 litters); malrotation of the right hindlimb (1 fetus/1 litter); and in the same litter, palatoschisis (1 fetus) and agenesis of claws of the hindpaw (1 fetus). These malformations are considered to be treatment-related based on their absence in the concurrent controls and on their absence (peromelia, palatoschisis, claw

agenesis) or low frequency (malrotation of hindlimb, 0-0.09%) in the historical controls.

Examination of the fetal heads by the Wilson technique revealed 1 fetus with hydrocephalus internus in the HDT. This malformation is considered to be treatment-related based on its absence in the concurrent controls and on its low frequency (0-0.1%) in the historical controls.

Skeletal examination of fetuses revealed, in the HDT only (Table 13), the occurrence of peromelia in 5 fetuses (4 litters). The associated findings included humerus reduced in size, radius/ulna reduced in size or vestigial, forepaw reduced in size or absent. These findings are considered treatment-related based on their absence in concurrent and historical controls. In addition, there was a small, consistent, but not statistically significant effect of tebuconazole upon the rate of ossification. Specific findings included increased nonossification of the phalanges in all 4 limbs, as summarized in Table 13. Abnormal ossification and fusion of sternebra was reported in the LDT (1 fetus) and the MDT (1 fetus) the effect does not appear to be dose related, however.

Based on the above observations this study defines a developmental toxicity NOEL of 30 mg/kg/day and a LOEL of 100 mg/kg/day.

Table 12. Cesarean Section Observations[a] in Rabbits.

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. animals assigned | 16 | 16 | 16 | 16 |
| No. animals mated/inseminated | 16 | 16 | 16 | 16 |
| Pregnancy rate, number(%) | 15(94) | 14(88) | 15(94) | 14(88) |
| Total corpora lutea | 128 | 125 | 140 | 132 |
| Corpora lutea/dam | 8.5 | 8.9 | 9.3 | 9.4 |
| Total implantations | 121 | 116 | 133 | 124 |
| Implantations/dam | 8.1 | 8.3 | 8.9 | 8.9 |
| Total live fetuses | 111 | 113 | 122 | 90 |
| Live fetuses/dam | 7.4 | 8.1 | 8.1 | 6.4[b] |
| Total resorptions | 10 | 3 | 11 | 34 |
| Early | 2 | 2 | 5 | 12[c] |
| Late | 8 | 1 | 6 | 22* |
| Resorptions/dam | 0.7 | 0.2 | 0.7 | 2.4 |
| Total dead fetuses | 0 | 0 | 0 | 0 |
| Total dead fetuses/dam | 0 | 0 | 0 | 0 |
| Mean fetal weight (g) | 35.1 | 33.5 | 35.0 | 33.0 |
| Preimplantation loss (%) | 5.5 | 7.2 | 5.0 | 6.1 |
| Postimplantation loss (%) | 8.3 | 2.6 | 8.3 | 27.4* |

[a] Data from pp 27, 30-32 of the Study Report (MRID 407009-45).
[b] This effect appears to be associated with a significantly increased rate of late ("fetal") resorptions in the HDT.
[c] The increase in the number of early resorptions was found by the authors to have a p-value of $p = 0.064$ (Not statistically significant).
* = $p<0.05$.

Table 13. Skeletal Observations in Rabbits. Data from MRID 407009-45.

| Observation | Dose | | | |
|---|---|---|---|---|
| | Control | LDT | MDT | HDT |
| No. pups (litters) exmd. | 111(15) | 113(14) | 127(15) | 90(14) |
| Malformations and/or Anomalies: | | | | |
| No. pups (litters): | | | | |
| Limbs | | | | |
| Peromelia (Left or right foreleg shortened or reduced to stump) | 0 | 0 | 0 | 5(4) |
| Perodactylia | 0 | 0 | 0 | 1(1) |
| Thorax | | | | |
| Abnormally ossified and fused sternebrae[a] | 0 | 1(1) | 1(1) | 0 |
| Broadened distal portion of rib | 0 | 0 | 1(1) | 0 |
| Other Skeletal Observations: | | | | |
| No. fetuses (% fetuses): | | | | |
| Left forelimb (Nonossified): | | | | |
| Total litters affected | 14 | 14 | 15 | 14 |
| Number of fetuses (% fetuses): | | | | |
| Digit 5 medial phalanx | 80(72) | 84(74) | 90(74) | 78(87) |
| Right forelimb (Incomplete, ossif.): | | | | |
| Total litters affected | 8 | 10 | 11 | 9 |
| Number of fetuses (% fetuses): | | | | |
| Digit 1 proximal phalanx | 6(5) | 7(6) | 4(3) | 13(14) |
| Digit 2 medial phalanx | 2(2) | 3(3) | 2(2) | 5(6) |
| Digit 4 medial phalanx | 16(14) | 19(17) | 26(21) | 21(23) |
| Left hindlimb (Nonossified): | | | | |
| Total litters affected | 9 | 10 | 9 | 10 |
| Number of fetuses (% fetuses): | | | | |
| Toe 4 medial phalanx | 17(15) | 22(19) | 23(19) | 36(40) |
| Right hindlimb (Nonossified): | | | | |
| Total litters affected | 8 | 10 | 8 | 11 |
| Number of fetuses (% fetuses): | | | | |
| Toe 4 medial phalanx | 16(14) | 21(19) | 22(18) | 35(39) |

[a] Sternebrae 2-4 in the LDT and sternebrae 4 and 5 in the MDT.

B. Reproduction Study

1. Two Generation Study in Rats -

Reference: HWG 1608, Two-generation study in rats. R. Eiben. November 12, 1987. Mobay Corporation, Agricultural Chemical Division (Sponsor). Toxicology Division, Bayer AG, Wuppertal, Friedrich-Ebert Str. 217-33 and PATCO AG, CH-4452 Itingen, Switzerland (Testing Facility). MRID 407009-46 . Core Classification: Minimum.

Technical Tebuconazole (95.2%) at concentrations of 0, 100, 300 or 1000 ppm was administered in the diet to groups of male and female Bor:WISW(SPF Cpb) Wistar rats (25 of each sex/dose group) for two consecutive generations.

a. Parental Toxicity

The NOEL for parental toxicity was 300 ppm. The LOEL for parental toxicity was 1000 ppm based on the following observations:

- There was a general increase in the reported incidence of toxicity signs for loss of hair in HDT F0 adult females (HDT/196 days vs control/123 days) and in HDT and MDT F1B adult females (HDT/72 days, MDT/63 days vs control/39 days).

- Mean body weights were consistently and statistically significantly depressed in both sexes at the HDT prior to and after mating, and during and after lactation in both the F0 and F1B parental generations (Table 14).

- There was a small, generally consistent but not statistically significant, depression in food consumption for the HDT males and/or females of both the F0 and F1B parents over the entire measurement period. Decreases amounted to approximately 10% (F0 males), 8% (F1B males), and 11% (F1B females) compared to the respective controls (Table 15).

- Statistically significant decreases in absolute kidney [F1b males (-10.3%) and females (-7.5%)], adrenal [F1b males (-11.3%) and liver weights [F1b males (-11.9%)] were observed at the HDT. Relative testes weight in HDT F1B males was statistically significantly increased (+ 8.1%).

- Increased severity of spleen hemosiderosis in F0 and F1b high-dose females. Although the incidence of spleen hemosiderosis in F0 males and females is close to 100% (Table 16), examination of the severity (grade) of the lesions indicates that HDT F0 females (grade 4 : 19/HDT vs 1/control, Table 16) had elevated findings as compared to controls. Likewise, HDT F1b females (grade 3: 9/HDT vs 1/control) had elevated findings as compared to controls.

Table 14. Mean body weights for F0 and F1b adults.

| Week on study | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| **F0 males:** | | | | |
| 0 | 92(7)[b] | 92(7) | 93(7) | 91(7) |
| 1 | 131(8) | 129(10) | 130(9) | 118(9)* |
| 17 | 351(25) | 343(22) | 348(24) | 327(23)** |
| 29 | 374(23) | 370(26) | 370(25) | 354(26)** |
| 34 | 380(24) | 381(25) | 380(25) | 364(25)** |
| **F0 females:** | | | | |
| 0 | 88(5) | 89(5) | 90(6) | 89(6) |
| 1 | 110(6) | 111(8) | 111(7) | 104(7)** |
| 17 | 206(14) | 208(17) | 206(16) | 196(17)* |
| d6[a] | 218(15) | 223(17) | 219(18) | 208(17)* |
| d20 | 284(24) | 282(33) | 288(36) | 263(35)* |
| 29 | 223(15) | 224(19) | 222(19) | 209(20)* |
| d6 | 234(17) | 240(22) | 233(21) | 218(23)* |
| d20 | 311(34) | 293(37) | 286(46) | 284(41)* |
| 34 | 263(15) | 255(25) | 249(25) | 233(25)** |
| **F1B males:** | | | | |
| 5 | 97(11) | 92(12) | 99(12) | 82(16)** |
| 14 | 317(36) | 317(35) | 321(27) | 286(32)** |
| 27 | 390(35) | 388(36) | 381(32) | 352(41)** |
| 31 | 390(35) | 391(36) | 390(34) | 356(42)** |
| **F1B females:** | | | | |
| 5 | 86(7) | 83(8) | 89(7) | 75(14)** |
| 14 | 192(14) | 192(16) | 195(13) | 180(17)** |
| d6 | 211(18) | 214(16) | 216(15) | 199(19)* |
| d20 | 278(33) | 286(31) | 290(26) | 265(32) |
| 27 | 219(15) | 222(17) | 224(14) | 206(17)** |
| d6 | 238(20) | 237(17) | 243(16) | 223(19)* |
| d20 | 298(35) | 302(45) | 314(36) | 278(32)* |
| 32 | 247(28) | 242(18) | 244(17) | 225(20)** |

[a] d = days after female insemination.
[b] mean in grams (standard deviation), data taken from pp 53-58 of the study report.
* $p < 0.05$; ** $p < 0.01$.

Table 15. Summary of food consumption data (g/animal/day)[a].

| Week on study F0(male/female) | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| 1 | 15.09/13.54 | 15.07/13.73 | 14.89/14.23 | 13.73/13.21 |
| 5 | 20.16/14.80 | 19.28/15.18 | 21.27/15.15 | 19.18/14.98 |
| 10 | 21.23/15.43 | 20.77/16.41 | 21.57/16.04 | 20.93/16.42 |
| 17 | 21.15/16.08 | 19.95/20.76 | 19.60/22.10 | 19.17/16.27 |
| Entire period (W1-W17) | 21/15 | 20/16 | 20/16 | 19/16 |
| F1B(male/female) | | | | |
| 6 | 16.98/15.81 | 16.41/14.54 | 16.04/13.19 | 14.83/13.33 |
| 10 | 25.00/18.47 | 24.46/19.31 | 25.39/20.31 | 23.94/18.75 |
| 15 | 24.58/18.90 | 23.88/17.31 | 24.70/18.37 | 22.23/15.99 |
| Entire period (W6-W15) | 24/19 | 24/18 | 24/19 | 22/17 |

[a] Food data up to first mating. Data for F0 obtained from pp. 78-79 of the study report; data for F1B obtained from p. 122 of the study report.

Table 16. Incidence and severity of spleen hemosiderosis in F0 and F1 adults[a].

| | Incidence at: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Control | | 100 ppm | | 300 ppm | | 1000 ppm | |
| | M | F | M | F | M | F | M | F |
| F0 adults | | | | | | | | |
| Number examined | 24 | 24 | 25 | 25 | 25 | 25 | 24 | 25 |
| Hemosiderosis incidence | 22 | 23 | 25 | 24 | 25 | 25 | 24 | 25 |
| Hemosiderosis severity: | | | | | | | | |
| Grade 2 | 9 | 11 | 10 | 7 | 7 | 5 | 3 | 0 |
| Grade 3 | 13 | 11 | 15 | 14 | 17 | 14 | 21 | 6 |
| Grade 4 (Most severe) | 0 | 1 | 0 | 3 | 0 | 4 | 0 | 19 |
| F1b adults | | | | | | | | |
| Number examined | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Hemosiderosis incidence | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 9 |
| Hemosiderosis severity: | | | | | | | | |
| Grade 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 9 |

[a] Data from pages 241c-293c of the study report.

b. Reproductive Toxicity

The NOEL for reproductive toxicity was 300 ppm. The LOEL was 1000 ppm, based upon neonatal birth weight depression. Neonatal weights (Table 17) from birth through weeks 3 or 4 of lactation were consistently and statistically significantly depressed at the high dose in all littering groups (F1a, F1b, F2a, and F2b); this effect is considered to be compound-related.

Although there was an apparent increase in the number of dead fetuses with respect to controls (Table 17) in the MDT and HDT of the F1a pups (5/control vs 16/MDT, 17/HDT), the increase was small in the F1b pups and was not consistent in the F2a and F2b pups.

A statistically significant decrease in the mean number of fetuses/litter at birth through week four of lactation was observed in both F1a and F1b at the HDT (5.1/HDT vs 7.2/Controls, F1a; 4.3/HDT vs 6.8/controls, F1b); this effect, however, was not observed for F2a and F2b pups (Table 17).

Although there were statistically significant changes in viability and lactation indices for the F1a and F1b pups (Table 18), these changes were not dose dependent, and did not occur in the F2a and F2b pups.

Table 17. Neonatal indices for the F0 and F1B generations[a].

| F0: F1a<br>Dose: | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| total # | 204 | 186 | 225 | 177 |
| # dead | 5 | 0 | 16 | 17 |
| #/litter(d0) | 9.0(1.7) | 10.3(2.9)* | 9.5(2.8) | 7.6(3.4) |
| #/litter(5DBR) | 8.9(0.8) | 9.3(2.7) | 9.0(3.1) | 6.7(3.7) |
| #/litter(5DAR) | 7.6(0.7) | 7.5(1.7) | 7.2(1.9) | 5.9(3.0) |
| #/litter(Wk 1) | 7.4(1.3) | 7.4(1.7) | 6.9(2.2) | 5.8(3.1) |
| #/litter(Wk 4) | 7.2(1.8) | 6.7(2.4) | 6.5(2.2) | 5.1(3.3)* |
| % males | 48 | 51 | 47 | 51 |
| Pup wt.(birth) | 6.0(0.5) | 5.7(0.5)* | 5.8(0.6) | 5.6(0.4)* |
| Pup wt.(5DBR) | 10.2(1.2) | 9.4(1.0) | 9.8(1.5) | 9.0(1.4)** |
| Pup wt.(5DAR) | 10.4(1.2) | 9.6(1.0) | 10.0(1.4) | 9.0(1.4)** |
| Pup wt. (Wk 1) | 12.6(1.9) | 12.4(1.6) | 13.2(2.2) | 10.7(2.2)** |
| Pup wt. (Wk 4) | 54.1(5.1) | 53.7(5.3) | 56.6(7.5) | 47.8(8.0)** |
| F0: F1b | | | | |
| total # | 210 | 159 | 151 | 160 |
| # dead | 9 | 8 | 12 | 12 |
| #/litter(d0) | 9.1(2.1) | 8.4(3.6) | 7.7(3.4) | 6.7(3.3)* |
| #/litter(5DBR) | 8.6(2.3) | 7.5(3.3) | 7.3(3.5) | 6.0(3.7)* |
| #/litter(5DAR) | 7.5(1.0) | 6.5(2.3) | 6.3(2.5) | 5.3(3.0)** |
| #/litter(Wk 1) | 7.4(1.0) | 6.1(2.6) | 6.3(2.5) | 4.9(3.0)** |
| #/litter(Wk 4) | 6.8(1.7) | 4.9(2.9)* | 6.2(2.5) | 4.3(3.0)** |
| % males | 50 | 49 | 47 | 51 |
| Pup wt.(birth) | 5.7(0.5) | 5.6(0.7) | 5.7(0.6) | 5.6(0.8) |
| Pup wt.(5DBR) | 9.3(1.2) | 8.5(1.6) | 10.2(1.9) | 8.9(1.9) |
| Pup wt.(5DAR) | 9.4(1.2) | 8.5(1.6) | 10.3(1.9) | 8.8(1.9) |
| Pup wt. (Wk 1) | 12.7(1.6) | 11.2(2.6) | 13.6(2.1) | 11.4(2.7)* |
| Pup wt. (Wk 4) | 58.7(10.1) | 58.6(8.6) | 60.2(8.8) | 52.4(8.8) |
| F1B: F2a | | | | |
| total # | 255 | 271 | 261 | 239 |
| # dead | 3 | 3 | 3 | 4 |
| #/litter(d0) | 10.5(2.0) | 11.2(1.0) | 11.2(2.1) | 10.2(1.5) |
| #/litter(5DBR) | 10.3(1.9) | 11.1(1.0) | 11.0(2.1) | 9.9(1.4) |
| #/litter(5DAR) | 7.9(0.6) | 8.0(0.0) | 7.9(0.3) | 7.9(0.5) |
| #/litter(Wk 1) | 7.8(0.6) | 8.0(0.0) | 7.9(0.3) | 7.8(0.5) |
| #/litter(Wk 4) | 7.7(0.7) | 8.0(0.2) | 7.9(0.3) | 7.7(0.8) |
| % males | 48 | 45 | 49 | 49 |
| Pup wt.(birth) | 5.9(0.6) | 5.5(0.3)** | 5.7(0.5) | 5.3(0.3)** |
| Pup wt.(5DBR) | 9.9(1.5) | 9.3(0.8) | 9.6(1.2) | 8.1(1.0)** |
| Pup wt.(5DAR) | 10.1(1.5) | 9.4(0.8)* | 9.7(1.2) | 8.1(0.9)** |
| Pup wt. (Wk 1) | 12.7(1.9) | 12.1(1.3) | 12.6(1.9) | 10.3(1.2)** |
| Pup wt. (Wk 4) | 56.0(6.1) | 56.4(4.2) | 56.4(5.6) | 43.7(5.0)** |
| F1B: F2b<br>Dose: | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
| total # | 214 | 253 | 273 | 213 |
| # dead | 8 | 5 | 11 | 10 |
| #/litter(d0) | 9.0(3.9) | 11.8(2.3)** | 11.4(2.4)* | 9.7(3.3) |
| #/litter(5DBR) | 8.2(4.0) | 11.3(2.0)** | 11.3(2.4)** | 8.8(3.9) |
| #/litter(5DAR) | 6.5(2.7) | 7.9(0.7) | 7.9(0.6) | 6.8(2.5) |
| #/litter(Wk 1) | 6.5(2.8) | 7.9(0.7) | 7.9(0.6) | 6.8(2.5) |
| #/litter(Wk 4) | 6.3(2.9) | 7.6(1.2) | 7.7(0.7) | 6.7(2.5) |
| % males | 45 | 43 | 50 | 51 |
| Pup wt.(birth) | 5.7(0.6) | 5.7(0.3) | 5.7(0.4) | 5.3(0.5)* |
| Pup wt.(5DBR) | 9.2(1.5) | 9.1(0.9) | 9.4(1.1) | 8.4(2.7)** |
| Pup wt.(5DAR) | 9.3(1.5) | 9.3(0.8) | 9.7(1.2) | 8.5(2.6)** |
| Pup wt. (Wk 1) | 12.6(2.0) | 12.0(1.3) | 12.6(1.7) | 10.0(1.1)** |
| Pup wt. (Wk 3) | 36.0(4.2) | 36.8(4.2) | 38.1(3.0) | 30.5(3.4)** |

[a] From pages 8 and 9 of the DER. 5DBR = day 5, before litter size reduction; 5DAR = day 5, after litter reduction; wk = week after birth. S.D. in parenthesis.

Table 18. Reproductive indices for the F0 and F1B generations

**F0 generations**

| Dose: | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| Parameters | F1a | F1b | F1a | F1b | F1a | F1b | F1a | F1b |
| # females | 25 | 23 | 25 | 25 | 25 | 25 | 25 | 25 |
| insemination index | 100 | 100 | 96.0 | 92.0 | 100 | 96.0 | 96.0 | 92.0 |
| gestation index | 100 | 100 | 100 | 94.4 | 100 | 100 | 90.5 | 95.5 |
| gesta. period(d) | 22.3 | 22.0 | 22.2 | 21.9 | 22.3 | 22.2 | 22.3 | 22.1 |
| fertility index | 88.0 | 95.7 | 75.0 | 78.3 | 88.0 | 75.0 | 87.5 | 95.7 |
| viability index | 98.5 | 94.5 | 90.3** | 89.4 | 95.2 | 94.2 | 88.1** | 88.5 |
| lactation index | 95.2 | 90.9 | 88.9 | 76.1** | 91.1 | 98.2* | 86.3* | 80.3* |
| # viable ltrs | 22 | 22 | 17 | 17 | 18 | 18 | 19 | 21 |
| # nonviable ltrs | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 |

**F1B generations**

| Dose: | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| Parameters | F2a | F2b | F2a | F2b | F2a | F2b | F2a | F2b |
| # females | 25 | 24 | 25 | 25 | 25 | 25 | 25 | 25 |
| insemination index | 100 | 100 | 100 | 100 | 96.0 | 100 | 100 | 100 |
| gestation index | 100 | 91.3 | 100 | 100 | 100 | 100 | 100 | 100 |
| gesta. period(d) | 22.3 | 22.1 | 22.0 | 21.7 | 22.1 | 21.7 | 22.0 | 22.1 |
| fertility index | 96.0 | 95.8 | 96.0 | 84.0 | 95.8 | 92.0 | 92.0 | 84.0 |
| viability index | 98.0 | 91.7 | 99.6 | 96.0 | 97.7 | 98.9** | 96.6 | 91.1 |
| lactation index | 98.4 | 97.3 | 99.5 | 97.0 | 99.5 | 97.2 | 97.2 | 97.9 |
| # viable ltrs | 24 | 21 | 24 | 21 | 23 | 23 | 23 | 21 |
| # nonviable ltrs | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

(Definitions of parameters:

Fertility index = $\frac{\text{number of pregnant females x 100}}{\text{number of mated females}}$

Gestation index = $\frac{\text{number females with live litters x 100}}{\text{number of pregnant females}}$

Viability index = $\frac{\text{number live pups after 5 days x 100}}{\text{number pups born alive}}$

Lactation index = $\frac{\text{number of live pups after 4 weeks x 100}}{\text{number of live pups after 5 days after reduction}}$

Insemination index = $\frac{\text{number of mated females x 100}}{\text{number paired females}}$

## III. ADDITIONAL TOXICOLOGY DATA

The following studies are acceptable or core minimum unless stated otherwise.

### A. Acute, Subchronic, and Chronic Toxicity Data

Acute oral $LD_{50}$ values were as follows (MRID 407009-17):

- o Rats: 5000 mg/kg (fasted males) and 3933 mg/kg (fasted females);
- o Mice: 1615 mg/kg (males) and 3023 mg/kg (females).

The acute dermal $LD_{50}$ in rats was > 5000 mg/kg, no signs of toxicity were reported at the dose tested (MRID 407009-17; this dermal study was classified as supplementary).

Administration of tebuconazole in the feed at concentrations of 100, 400, and 1600 ppm for 13 weeks resulted in decreased mean body weights and mean body weight gains in male and female Wistar rats of the high-dose group (MRID No. 407009-30). An increased incidence of vacuole formation in zona fasciculata cells in the adrenals of high-dose animals of both sexes and in females fed 400 ppm was demonstrated. Similarly, high dose males and females had increased incidences of hemosiderosis. Both lesions were reported by the study author to be treatment related. Adverse compound effects appeared to be more intense in females than in males and were attributed to increased female food consumption. In males the LOEL is 1600 ppm based on decreased body weights and body weight gain and histological changes; the NOEL is 400 ppm. In females the LOEL is 400 ppm and the NOEL is 100 ppm.

Administration of tebuconazole in the feed at concentrations of 200, 1000, or 5000 ppm for 13 weeks resulted in decreased mean body weight, body weight gains, and food consumption in beagle dogs of the mid- and high-dose groups (MRID No. 407009-34). Other findings in high-dose animals included compound-induced lens opacity, anisocytosis, and increased siderosis of the liver and spleen. Effects on the liver included increased alkaline phosphatase, decreased albumin, increased cytochrome P-450 at the high dose and a dose-related increase in N-demethylase activity. Increased vacuolation in the adrenals of females was considered to be compound related by the study authors. This study defines a LOEL of 1000 ppm, based on decreases in mean body weights, body weight gains, and food consumption and on increases in N-demethylase activity; the NOEL is 200 ppm.

Tebuconazole was administered to Wistar rats in the feed at concentrations of 0, 100, 300, and 1000 ppm for 2 years (MRID No. 407009-39). Statistically significant effects in mid- and high-dose females included depression in body weights (4-5% and 7-9%, respectively) throughout the dosing period and an alteration in hematological parameters. In addition, there was a statistically significant elevation of liver microsomal enzymes (assessed microscopically) at all dose levels and a dose-related decrease in female adrenal weights in association with a dose-related decrease in adrenal cortical degeneration. In males there was a statistically significant elevation in the combined incidences of thyroid C-cell adenoma, carcinoma, and hyperplasia, but not of adenoma or carcinoma alone. The incidences were, however, within the historical control

range. Statistically significant weight loss in males was limited to the initial weeks of the study. Male rats had a statistically significant elevation in the combined incidences of thyroid C-cell adenoma, carcinoma and hyperplasia but not of adenoma or carcinoma alone. The incidences were, however, within the historical control range.

Tebuconazole was administered to beagle dogs of both sexes at dietary concentrations of 0, 40, 200 and 1000 (1-39 weeks)/2000 (40-52 weeks) ppm for 52 weeks (MRID No. 407009-41). The treatment caused lenticular and corneal opacity in mid- and high-dose animals. The liver appeared to be a target organ, based on elevations in alkaline phosphatase (HDT both sexes), N-demethylase activity and triglycerides (HDT, both sexes), iron-containing pigments (MDT, HDT) in addition to gross changes in liver appearance (MDT, HDT). Other tissues/organs affected included included blood (anisocytosis), adrenals (increased vacuolation in zona fasciculata), kidney and spleen (elevated weights) at mid- and/or high-dose levels. The systemic LOEL is set at 200 ppm, based upon ocular lesions and hepatic toxicity in either sex at the mid- and high-dose levels. The NOEL is set at 40 ppm.

Tebuconazole was administered to NMRI mice of both sexes at dietary concentrations of 0, 20, 60, or 180 ppm for 21 months (MRID No. 407009-41). There was slight depression in body weight in males during the first third of the study; there was no apparent body weight depression in females. The major target organ was found to be the liver in both sexes, with elevations in bilirubin and liver weights in the mid- and high-dose groups, in addition to increased incidence of minimal centrilobular and periportal vacuolation and lipid deposition. Mid- and high-dose males had an increase in adrenal cortical cell size and hyperplasia. Mid- and high-dose females had increases in minimal extramedullary hemopoiesis and in sinusoidal cellularity in the liver plus an increase in minimal interstitial edema of the pancreas. Both sexes had an elevation in stomach gastritis (HDT). A slight elevation in benign liver tumors was reported, but this incidence was within the historical control range for six studies. This study is classified was CORE supplementary on the basis that the MTD was not reached.

Because the MTD was not reached in the above mouse oncogenesis study (MRID No. 407009-41), the following mouse oncogenesis study was conducted at higher doses (MRID 421750-01):

HWG 1608 was administered to Bor:NMRI(SPF-Han) mice of both sexes for a period of up to 91 weeks in the diet at levels of 0, 500, and 1500 ppm resulting in mean respective compound intakes of 0, 84.9 and 279 mg/kg body weight/day (males) and 0, 103.1, and 356.5 mg/kg body weight/day (females). Statistically significantly decreased body weights and increased food consumption were reported that were consistent with decreased food efficiency at 500 and 1500 ppm in males and at 1500 ppm in females. Clinical chemistry values (dose-dependent increases in plasma GOT, GPT and AP) for both sexes were consistent with hepatotoxic effects at both 500 ppm and 1500 ppm. Relative liver weight increases reached statistical significance at both 500 and 1500 ppm in males and at 1500 ppm only in females. Histopathology included dose-dependent increases in hepatic panacinar fine fatty vacuolation, statistically significant at 500 and 1500 ppm in males and at 1500 ppm in females. Other histopathology included significant

oval cell proliferation in both sexes at 1500 ppm and dose-dependent ovarian atrophy that was stat. significant at 500 and 1500 ppm. The foregoing evidence indicated that the MTD was achieved at or around 500 ppm. Neoplastic histopathology consisted of statistically significant incidences of hepatocellular neoplasms: adenomas (35.4%) and carcinomas (20.8%) at 1500 ppm in males and carcinomas only (26.1%) at 1500 ppm in females.
In addition, there was a dose-related, but not statistically significant, increase in histiocytic sarcomas in both sexes. In males the incidences amounted to 2.1%, 4.2% and 6.3% at 0, 500 and 1500 ppm, respectively. In females the incidences amounted to 2.1%, 6.7%, and 10.9% at 0, 500 and 1500 ppm, respectively. This study was graded CORE supplementary pending submission of pertinent historical control data on histiocytic sarcomas.

B. Mutagenicity Data

Tebuconazole has been tested in several mutagenicity studies. The acceptable tests fulfill requirements for all three categories. These categories are: gene mutations, structural chromosomal aberrations, and other genotoxic effects (e.g. DNA damage and repair)

a) Salmonella assay: Negative in 1 acceptable Salmonella reverse mutation assay ± metabolic activation (MRID 407009-47 and 407009-48).

b) Mouse micronucleus test, for structural chromosomal aberrations: Negative in 1 acceptable assay (MRID 407009-51).

c) Sister chromatid exchange (CHO cells) : Negative in 1 acceptable assay (MRID 407009-52).

d) Unscheduled DNA synthesis, for DNA damage: Negative in 1 acceptable UDS/primary mouse hepatocyte assay (MRID 408164-02).

Tebuconazole was negative in the following unacceptable asssays: CHO/HGPRT forward mutation assay (MRID 407009-49), dominant lethal test (MRID 407009-50), in vitro cytogenetic with human lymphocytes (MRID 407009-53), E.coli DNA damage/repair (407009-55).

The weight of the evidence does not suggest a mutagenicity concern for tebuconazole.

C. Metabolism/Pharmacokinetic Data

The metabolism of $^{14}C$-labeled tebuconazole technical after oral dosing was studied in Wistar rats of both sexes (MRID Nos. 409959-11 and 409959-12). When [phenyl-UL-$^{14}C$]-labeled tebuconazole was administered as a single oral dose of 2 or 20 mg/kg to male and female Wistar rats, the compound was rapidly and extensively absorbed, extensively metabolized, and rapidly excreted. Over 98% of a single oral dose of [phenyl-UL-$^{14}C$]-labeled tebuconazole (2mg/kg) was absorbed from the GI tract, based on [$^{14}C$] excretion in urine (7.4% of the dose) and in bile (90.68% of the dose), as determined in bile-fistulated male rats. In intact rats, over 86-98% of the administered radioactivity was excreted by 72

hours. About 14-16% and 72-82% of the dose appeared in urine and feces, respectively, in males and about 28-32% and 62% of the dose appeared in urine and feces, respectively, in females. Tissue concentrations were highest in liver at sacrifice, 72 hours after dosing. Tebuconazole undergoes extensive metabolism in rats. A total of 10 compounds were identified in excreta, amounting to 51-58% of the dose in males and to 68-71% of the dose in females. The untransformed parent compound amounted to 0.5-2.2% of the dose. A large fraction of the identified metabolites corresponded to successive stages in the oxidation of one of the methyl groups in the t-butyl moiety of tebuconazole. Dose-dependent changes in metabolite ratios of tebuconazole are suggestive of changes in detoxication patterns at the high dose; these may result from metabolic saturation. This study was conditionally classified as supplementary.

The dermal absorption of technical tebuconazole was studied in adult male Sprague Dawley-derived rats (MRID 409959-13). Four groups of rats were dosed with tebuconazole technical (in ethanol) at nominal doses of 0.01, 0.1, 1 and 10 mg/rat (actual doses of 0.604, 5.85, 52.4 and 547 $\mu g/cm^2$, respectively) and dermal absorption of test material was assessed at 0.5, 1, 2, 4, 8 and 24 hours of exposure. At 8 hours of exposure, the fraction of the dose absorbed ranged from 1.45% at the high dose to 8.01% at the lowest dose; the fraction of the dose remaining in the skin after washing (and thus is potentially absorbable) ranged from 66.44% at the highest dose to 42.26% at the lowest dose. It is noted that in this study tebuconazole was dissolved in ethanol, an organic solvent, and thus the degree of dermal absorption observed in this study may be different (possibly greater) to that obtainable using an aqueous suspension of the test material.

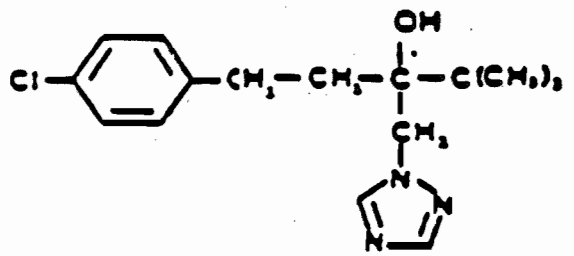
D. Structure Activity Relationships

Tebuconazole is structurally related to the compounds listed in Figure 1. Maternal and developmental toxicity NOEL/LOEL values (from CORE minimum, guideline, or supplementary studies) for these compounds are listed in Table 19.

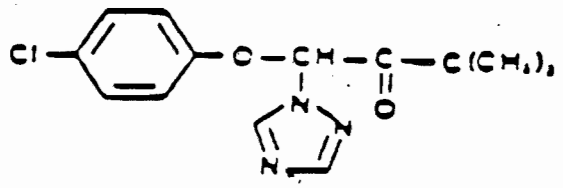
As shown in Table 19 bitertanol (Baycor), propiconazole and hexaconazole [in CORE minimum studies] and triademenol (Baytan) and uniconazole [in CORE supplementary studies] showed a developmental LOEL, below the maternal toxicity LOEL in rats. In addition, triadimefon (Bayleton), hexaconazole, and cyproconazole [in CORE supplementary studies] showed a developmental LOEL, below the maternal toxicity LOEL in rabbits.

Bitertanol (Baycor) was found to exhibit stunting and sternal anomalies, hexaconazole and uniconazole induced extra ribs, and propiconazole induced ossification retardation. The EPA Peer Review Committee agreed to classify uniconazole as a developmental toxicant on 9/7/90. Developmental effects observed in rats include cleft palate (triadimefon), increased resorptions and reduced mean fetal weights (azaconazole), and dose-dependent incidence of supernumerary ribs (cyproconazole).

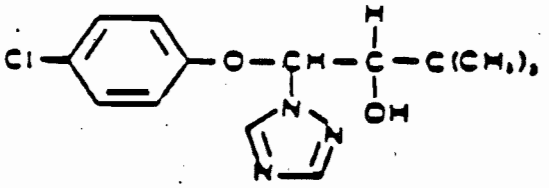
Appendix 10 has selected 1-liners for the compounds in Figure 1.



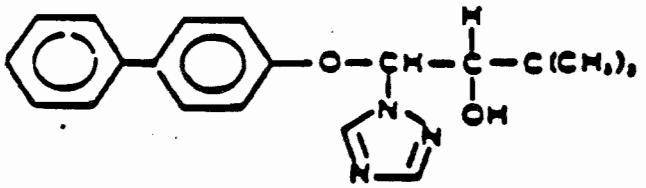
Terbuconazol
(Folicur)



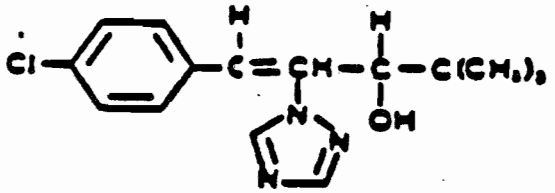
Triadimefon
(Bayleton)



Triademenol
(Baytan)

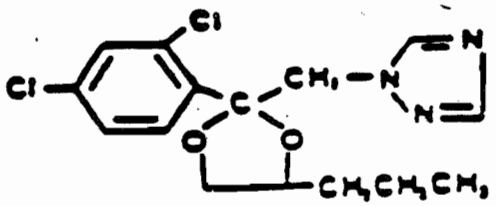


Bitertanol
(Baycor)

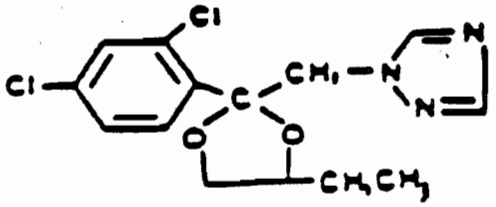


Uniconazole
(Prunit)

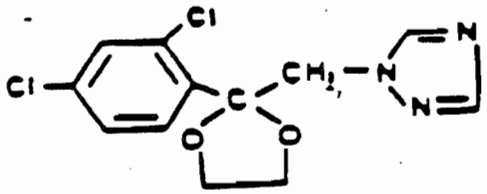
Figure 1. Tebuconazole and Structurally Related Compounds



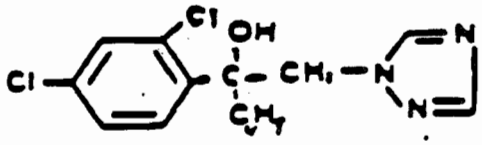
Propiconazole
(Tilt)



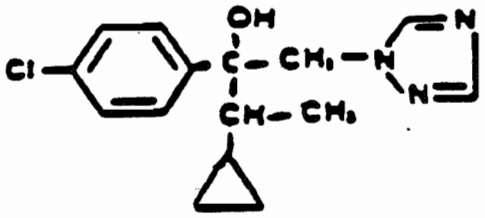
Etaconazole
(Vangard)



Azaconazole



Hexaconazole
(Anvil)



Cyproconazole
(SAN 619F)

Figure 1. Tebuconazole and Structurally Related Compounds (Cont.)

Table 19. Maternal and Developmental Toxicity NOEL/LOEL Values for Structurally Related Compounds[a].

| | | Developmental Toxicity | | |
|---|---|---|---|---|
| Chemical | Species | Maternal NOEL/LOEL (mg/kg/day) | Develop. NOEL/LOEL (mg/kg/day) | (CORE)[b] Remarks |
| Triadimefon | Rat | 10/25 | 50/100 | (M) Cleft palate |
| (Bayleton) | Rat | 10/30 | 50/75 | (M) Cleft palate |
| | Rabbit | >50 (HDT) | >50 (HDT) | (M) No effect reported at the HDT (50mg/kg/day). |
| | Rabbit | 10/30 | 30/100 | (S) Increased fetal resorptions at 100 mg/kg/day |
| | Rabbit | 50/120 | 20/50 | (S) Dose dep. incr. in incomplete ossificat.; plus rud./missing tails, extra ribs at HDT. |
| Triademenol | Rat | 5/15 | <5/5 | (S) Develop. NOEL is tentative. |
| (Baytan) | Rat | 30/60 | >30/No data | (S) Additional data required. |
| | Rabbit | >100 (HDT) | >100 (HDT) | (S) No effect reported at the HDT (100 mg/kg/day) |
| | Rabbit | 8/40 | 40/200 | (S) Red. fetal body weights and increased incidence of skeletal findings at 200 mg/kg. |
| Bitertanol | Rat | 30/100 | 10/30 | (M) Stunting and slight bone anomalies of the sternum at 30 mg/kg/day. Cleft palate, kinked tail, rib dysplasia at 100 mg/kg/day. |
| (Baycor) | Rat | 10/25 | 10/25 | (S) Delayed ossif. of sternebra and incr. incidence of lumbar ribs at 25 mg/kg/day. |
| | Rabbit | 30/100 | 30/100 | (M) Incr. resorptions, red. fetal weights at 100 mg/kg/day. |
| | Rabbit | 30/100 | 30/100 | (S) Lower mean fetal weight at 100 mg/kg/day, plus 1 club foot, 2 cleft palate, and 4 pigeon chest. |
| | Rabbit | 50/150 | 50/150 | (M) Specific effects not listed in the 1-liner. |

(Continued)

Table 19. Maternal and Developmental Toxicity NOEL/LOEL Values for Structurally Related Compounds (Contd).

| | Developmental Toxicity | | | |
|---|---|---|---|---|
| Chemical | Species | Maternal NOEL/LOEL (mg/kg/day) | Develop. NOEL/LOEL (mg/kg/day) | (CORE)[b] Remarks |
| Uniconazole[c] | Rat | 5/25 | 1/5 | (S) Extra cervical ribs at 5 mg/kg/day; incr. incidence of 14th. rib at 25 and 50 mg/kg/day. |
| | Rabbit | 10/20 | 20 (HDT) | (M) Develp. NOEL = 20 mg/kg/day. |
| Propiconazole | Rat | 100/300 | 30/100 | (M) Ossification retardation at 100 mg/kg/day. |
| (Tilt) | Rat | 30/90 | 30/90 | (M) Incr. incidence of of unossified sternebrae, rudimentary ribs, shortened or absent renal papillae at 90 mg/kg/day. |
| | Rabbit | 100/250 | >400 (HDT) | (M) Develop. NOEL > 400 mg/kg/day. |
| Etaconazole | Rat | >360 (HDT) | >360 (HDT) | (M) No effect reported at the HDT (360 mg/kg/day). |
| | Rabbit | 10/60 | 10/- | (M) Developmental LOEL not specified in 1-liner, presumably 60 mg/kg/day (MDT), for fetotoxicity. |
| Azaconazole | Rat | 10/40 | 40/160 | (S) Increased No. of resorption and red. mean fetal weight 160 mg/kg/day. Mortality at HDT = 67%. Bone anomalies assessment done radiographically (decreased sensitivity). |
| | Rabbit | >80 (HDT) | >80 (HDT) | (S) NOELs > HDT. |
| | Rabbit | - | - | (S) At 160 mg/kg/day: Anouria in 2/45 fetuses and 13th pair of ribs in 20/45 fetuses vs 14/112 in controls (p=2.8E-5). No NOEL or LOEL defined. |

(Continued).

Table 19. Maternal and Developmental Toxicity NOEL/LOEL Values for Structurally Related Compounds.

| | | Developmental Toxicity | | | |
|---|---|---|---|---|---|
| Chemical | Species | Maternal NOEL/LOEL (mg/kg/day) | Develop. NOEL/LOEL (mg/kg/day) | (CORE)[b] | Remarks |
| Hexaconazole | Rat | 25/250 | <2.5/2.5(LDT) | (G) | Delayed skeletal ossif. and extra 14th. ribs at 2.5 mg/kg/day. At higher doses, abnormalities of the urogenital system. |
| | Rabbit | 50/100 | 25/50 | (S) | Early intrauterine death at 50 mg/kg/day. |
| Cyproconazole | Rat | 6/12 | 6/12 | (M) | Incr. incid. of supernumerary ribs (dose-dependent). Hydrocephaly at 24 (1 fetus) and at 48 (2 fetuses) mg/kg/day. Cleft palate (2 fetuses, 2 litters) at 48 mg/kg/day. |
| | Rabbit | 10/50 | <2/2 | (S) | Hydrocephalus internus observed at all dose levels. Incr. inc. of fetal resorptions at 10 mg/kg/day. Agenesis of left kidney and ureter at 50 mg/kg/day. |

[a] Data obtained from the One-Liners for the indicated analogue. Invalid or Pilot studies were not selected.
[b] CORE - CORE Classification: G - Guideline, M - Minimum, S - Suplementary.
[c] EPA Peer Review Committee agreed on 9/7/90 that uniconazole should be classified a developmental toxicant.

## IV. STRENGTH OF THE EVIDENCE

### A. Summary of the Evidence

Table 20 summarizes NOEL/LOEL values for developmental/reproductive and maternal toxicity.

1. All three species tested (mice, rats and rabbits) showed developmental effects when tested via the oral route.

2. Evidence of some degree of developmental toxicity via the dermal route was observed in mice but not in rats.

3. Developmental/reproductive effects occurred at or higher than maternally toxic doses.

4. The lowest oral developmental NOEL/LOEL pair of values (10/30 mg/kg/day) corresponds to the mouse and the highest oral developmental NOEL/LOEL pair of values (30/100 mg/kg/day) corresponds to the rabbit. Rats have an intermediate pair of NOEL/LOEL pair values (30/60 mg/kg/day).

5. Reproductive effects (e.g. neonatal birth weight depression) were observed in rats in a two-generation reproduction study at dietary levels of tebuconazole of 1000 ppm (approximately 72-97 mg/kg/day).

6. Related conazole analogs have shown developmental effects in rats and rabbits.

### B. Strength of the Evidence

1. Dosing appears to have been adequate for the oral tests. Testing via the oral route was conducted at levels which are maternally toxic at the high dose but not so at the low dose.

2. Although there is evidence that dermal dosing was adequate in the case of the mouse, there is no evidence that adequate dermal dose delivery was achieved in the case of rats.

### C. Questions for the Peer Review Committee

1. The Committe is requested to comment on the significance, if any, of the developmental effects that occur in the three species at maternally toxic oral doses following in-utero exposure to tebuconazole.

2. What is the developmental toxicity potential of tebuconazole following dermal exposure, based on the results in mice and rats?

3. Will an additional risk assessment be required since an unacceptable MOE was determined for field workers using:

- o The NOEL obtained from a mouse oral developmental toxicity study.
- o Dermal penetration studies in rats using ethanol as a dosing vehicle.

4. Will additional data be required to assess the developmental toxicity potential of tebuconazole (e.g. bioavailability following dermal dosing in rats and mice).

Table 20. Summary of NOEL/LOEL values for developmental/reproductive and maternal toxicity data for tebuconazol.

| Species | Dose (mg/kg/day) | Maternal Toxicity NOEL/LOEL (mg/kg/day) | Maternal Toxicity Remarks | Developmental/Reproductive Toxicity NOEL/LOEL (mg/kg/day) | Developmental/Reproductive Toxicity Remarks | CORE |
|---|---|---|---|---|---|---|
| | | | **Developmental Toxicity** | | | |
| Mouse NMRI/ORIG Kisslegg | Oral (gavage); Main Study: 0, 10, 30, 100. Supplem. Study: 0,10, 20, 30, 100 | 10/20 | From supplementary study:<br>- Decreased mean corpuscular volume at 20-100 mg/kg/day.<br>- Decreased hematocrit at 30-100 mg/kg/day<br>- Hepatic vacuolation at 100 mg/kg/day | 10/30 | - Dose-dependent increase in runts/dam with $p \leq 0.05$ at 30 and 100 mg/kg/day.<br>- Statistically significant increase in no. of malformed fetuses/litter at 100 mg/kg/day. | Minimum |
| Mouse NMRI/KFM/ HAN | Dermal; Main Study: 0, 100, 300, 1000. Supplem. Study: 0, 100, 300, 1000. | 30/60 | From supplementary study:<br>- Liver microsomal enzyme activities increased ($p \leq 0.01$) at 300 and 1000 mg/kg/day.<br>- Dose-depend. increase in incidence and severity of fatty deposition in liver at 300 and 1000 mg/kg/day.<br>- Dose-depend. increase in ALT, with $p \leq 0.05$ at 1000 mg/kg/day | 300/1000 | - Statistically significant increases in skeletal variations coupled to marked increases in their litter incidences (e.g. bipartite sternebra 20% litters in controls increased to 40% at 1000 mg/kg/day). | Minimum |
| Rat Wistar/HAN (Kfm WIST, Outbred SPF) | Oral (gavage); 0, 30, 60 and 120. | 30/60 | - Daily food consumption on days 6-16 decreased ($p \leq 0.05$) at MDT (-7%) and HDT (-15%).<br>- Dose-dependent increase in relative liver weight with $p \leq 0.01$ at MDT and HDT. | 30/60 | - Dose-dependent increase in litter and fetal incidences of non-ossified vertebral arch with $p \leq 0.05$ at the MDT and HDT.<br>- Dose-dependent increase in fetal incidences of non-ossified digit 4 proximal phalanxes with $p \leq 0.05$ for litters at the MDT and HDT.<br>- Increased litter incidence of supernumerary ribs at MDT and HDT.<br>- Missing tail [1/232 fetuses] plus anopthalmia, agnathia and microstomia [1/232 fetuses] limited to the HDT. | Minimum |

**Appendix 1.** Mouse Oral Developmental Toxicity Study.

Appendix 1. Mouse Oral Developmental Toxicity Study.

Reviewed by: James N. Rowe, Ph.D. James N. Rowe 12/22/88
Review Section I
Toxicology Branch: Herb. Fung. Antimicroial Support (TS-769C)
Secondary Reviewer: Quang Q. Bui, Ph.D.
Review Section I, Tox. Branch: H.F.A.S. (TS-769C) Quang Bui 12/23/88

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity Guideline Section 83-3 TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 408215-00

TEST MATERIAL: HWG 1608 Technical

SYNONYMS: Folicur@; terbuconazole

STUDY NUMBER: Bayer report no. 16527; T5021859; Lab. Proj. no. 97411

SPONSOR: Mobay Corporation, Agricultural Chemicals Division
TESTING FACILITY: BAYER AG, Fachbereich Toxikologie, Institute of Toxicology/Agriculture Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, FRG

TITLE OF REPORT: HWG 1608, Study of embryotoxic effects on mice after oral administration

AUTHOR(S): Dr. M. Renhof

REPORT ISSUED: March 14, 1988

CONCLUSIONS: Oral gavage of terbuconazole at 0, 10, 30, 100 mg/kg to mice during days 6-15 of gestation did not produce any overt signs of maternal toxicity. However, results from an associated study (T5025712; 97411) tentatively indicated hepatic changes at all dose levels tested (increased release of AST, ALT, AP associated with liver weight increases and altered metabolic/physiology-increased mitosis, vacuolation and lipidosis); as well as a reduction in hematocrit at dose levels of 20-100 mg/kg/day. Developmental toxicity was noted at the mid and high dose levels in the form of retarded growth, increased numbers of runts (fetuses weighing less than 1.3 gm). In addition, the compound produced frank malformations (skull, "neural tube") at the HDT associated with a reduced rate of ossification in the cranium as compared to controls. The maternal toxicity NOEL is set at 10 mg/kg/day and the LOEL is set at 20 mg/kg/day (reduction in hematocrit). The developmental NOEL, based upon increase number of runts, is 10 mg/kg (LDT) and the LOEL is 30 mg/kg.

CLASSIFICATION: CORE MINIMUM

A. MATERIALS

(A photocopy of the materials and methods section is appended).

Test compound: Purity: 93.6%
Description: colorless crystals
Lot No: 1616002/84
Contaminants (list in CBI appendix): N/A

Vehicle(s): Distilled water with 0.5% Cremophor EL (BASF)

Test animals: Species: mice
Strain: NMRI/ORIG Kisslegg
Source: IVANOVAS
Age: males, sexually mature; females, sexually mature (nulliparous)
Weight: Males, > or = 25 gms; Females, 28-39 gms

B. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of terbuconazole, when administered by gavage from gestational days 6 through 15, inclusive.

Mating:

After acclimatization for at least 6 days, 2-3 females were housed with one male for approximately 4 hours during the day. If a vaginal plug was found, this day was designated Gestation day 0.

Group Arrangement:

| Test group | Dose level(mg/kg) | Number assigned |
|---|---|---|
| Control | 0 | 25 |
| Low dose | 10 | 25 |
| Mid dose | 30 | 25 |
| High dose | 100 | 25 |

Dosing:

All doses were in a volume of 5 ml/kg of body weight/day prepared daily during the dosing period. The dosing solutions were analyzed for stability and homogeneity. Dosing was based on body weights adjusted daily during the treatment period and was performed each day between 10 a.m. and noon.

Observations

The animals were checked for mortality or abnormal condition daily. Body weights were determined during the treatment period and the entire gestation period. Dams were sacrificed on day 18 of gestation. Gross macroscopic examination of all internal organs was performed at sacrifice. At C-section the following examinations were performed: number of implantations, number of live and dead fetuses/embryos (dams without live fetuses were classified as not pregnant-reason not stated, but not relevant since no dams died during the study), the sex of all live fetuses, individual and mean fetal weights per litter and of stunted fetuses, total and mean placental weight per litter, external malformations, visceral malformations by modified method of Wilson, and evisceration and clearing in potassium hydroxide and staining with alizarin red S for skeletal examinations.

Statistical Analysis

The following statistical analysis methods were used:

0 Nonparametric Wilcoxon rank-sum test (U-test of MANN-WHITNEY and WILCOXON), e.g., for body weight gains, number of implantations, number of fetuses and number of resorptions

0 Chi-square test (correction of YATES), e.g., for number of stunted fetuses

0 Chi-square test (correction of YATES or as Fisher's exact test, depending on frequency anticipated for indices of fertilized and pregnant animals.

Compliance

- A signed Statement of No Confidentiality Claim was provided.

- A signed Statement of Compliance with EPA GLP's was provided.

- A signed Quality Assurance Statement was provided.

C. RESULTS

1. Maternal toxicity

Mortality

No deaths in any dose group were reported.

Clinical observations

No abnormal signs of compound-related toxicity were reported.

Body weight

The investigators supplied the following data: individual body weights for day 0, 6-18 and mean body weight gains for days 6-15 and day 0-18 of gestation. Mean body weights during dosing and gestation are presented below:

Table I: Mean body weight gains (grams)[a]

| | Dosing Period (day 6-15) | Gestation period (day 0-18) |
|---|---|---|
| Group: | | |
| Control | 12.8 | 23.0 |
| LDT | 13.4 | 24.9 |
| MDT | 13.7 | 24.6 |
| HDT | 13.4 | 24.9 |

[a] = data extracted from p.12 of report

There was no evidence of a compound-related effect in the treated dams during the dosing period or during the entire gestation period.

Food consumption

Daily food consumption data was not submitted. Based upon the mean body weight gains it is unlikely that this would have been affected by compound administration.

Gross Pathological Observations

See discussion under observations.

2. Cesarean data are presented below (Table II):

Pregnancy rates ranged from 80% in the HDT to 96% in the control. Implantations/dam and live fetuses/dam were not significantly different among the dose groups. Total resorptions (#/dam) were somewhat elevated in the HDT as compared to the control group due to an increase in late resorption (0.8/control vs 1.3). This was not a statistically significant effect however--probably due to the large standard deviation in the HDT. Mean fetal weight in the HDT also appeared to be lower than the controls (1.36 gm/control vs 1.30/HDT). This is consistent with the observation of an increase in runts ( defined on p. 18 of report as weighing less than 1.13 gm;statistically significant, $p<0.05$) in the MDT and HDT as compared to controls. Mean placental weight was slightly but statistically significantly increased in the HDT as compared to controls. Sex ratios (% males) were not different among the dose groups.

Tables III and IV present malformations and skeletal changes observed in the fetuses examined.

There was a statistically significant increase in the total number of malformations observed at the HDT as compared to the control groups with increased malformation rate being evident in the skull (cleft palate, micrognathia, partial dysplasia of parietal bone) and the "neural tube" (enlargement of ventricle, asymmetry of verterbral bodies, dysplasia/abnormal spinal column) (1 fetus/1 litter in control vs 10 fetuses/8 litters). There was an elevation in the number of fetuses/dam with rudimentary ossification centers of the cranium in the HDT vs controls (1/1 in control vs 5/4 in HDT) which is not surprising in light of the malformations of the skull observed.

Cesarean Section Observations:

Table II: Cesarean Section Observations[a]

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #animals assigned | 25 | 25 | 25 | 25 |
| #animals mated/inseminated | 25 | 25 | 25 | 25 |
| Pregnancy rate (%) | 24(96) | 23(92) | 23(92) | 20(80) |
| Maternal wastage | | | | |
| #died | 0 | 0 | 0 | 0 |
| #died/pregnant | 0 | 0 | 0 | 0 |
| #non pregnant | 1 | 2 | 2 | 5 |
| #aborted | 0 | 0 | 0 | 0 |
| #premature delivery | 0 | 0 | 0 | 0 |
| Total corpora lutea | ---- | ---- | ---- | ---- |
| Corpora lutea/dam | | | | |
| Total implantations | 255 | 258 | 247 | 228 |
| Implantations/dam | 10.6 | 11.2 | 10.7 | 11.4 |
| Total live fetuses | 236 | 235 | 235 | 202 |
| Live fetuses/dam | 9.8 | 10.2 | 10.2 | 10.1 |
| # examd by Dawson method | 168 | 161 | 166 | 142 |
| # examd by Wilson method | 68 | 73 | 68 | 60 |
| Total resorptions | 19 | 23 | 12 | 27 |
| Early | 0.08 | 0.30 | 0.04 | 0.00 |
| Late | 0.71 | 0.70 | 0.48 | 1.25 |
| Resorptions/dam (S.D.) | 0.80(1.0) | 1.0(1.6) | 0.5(0.8) | 1.3(2.2) |
| Mean fetal weight(g) | 1.36(.08) | 1.37(.07) | 1.37(.13) | 1.30(.12) |
| Mean placental wt.(g) | 0.10(.01) | 0.10(.01) | 0.10(.02) | 0.11(.01)* |
| Postimplantation loss(%) | 7.4 | 8.9 | 4.9 | 11.4 |
| Sex Ratio (% Male) | 50.8 | 54.0 | 48.1 | 47.5 |
| Mean fetuses/dam (S.D.) | | | | |
| -minor skel. devia. | 0.08(.28) | 0.05(.21) | 0.17(.49) | 0.40(.68) |
| -malformations (all) | 0.04(.20) | 0.18(.66) | 0.0(0.0) | 0.65*(.93) |
| -runts | 0.21(.51) | 0.18(.50) | 0.91*(1.7) | 1.20*(2.12) |
| -# runts/dose group | 5 | 4 | 21 | 24 |

[a] = Data extracted from pp. 27-32, Tables 1-5
* significantly different from controls ($p<0.05$)

Table III: External/visceral malformations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| total# fetuses(ltrs) exmd | 236(24) | 234(23) | 234(23) | 202(20) |
| # " " (" ) affected | 1(1) | 4(2) | 0(0) | 13(8) |
| visceral:fetuses/ltr | 68(24) | 73(23) | 68(23) | 60(20) |
| TYPE | | | | |
| multiple: cleft face, palate, jaw; dysplasia of limbs; deformed spinal column, ribs; shortened tail | 1(1) | ---- | ---- | ---- |
| -skull: cleft palate, micrognathia, partial dysplasia parietal bone | ---- | 4(2) | ---- | 7(6) |
| -neural tube: brain ventricle enlarged, asymmetry vertebral bodies, dysplasia spinal column, abnormal flexion spinal column | ---- | ---- | ---- | 5(4) |
| -fused ribs, floating ribs | ---- | 1(1) | ---- | 1(1) |
| -tail: kinked, shortened | ---- | ---- | ---- | 1(1) |

Skeletal Examinations

Table IV: Skeletal Examinations (Dawson)

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # fetuses(ltrs) examined | 168(24) | 161(23) | 166(23) | 142(20) |
| STERNUM (#fetuses/#litters) | | | | |
| -ossif. ctrs missing; slightly cleft sternum | 1(1) | ---- | ---- | ---- |
| CRANIUM | | | | |
| -rudimentary ossif. ctrs. | 1(1) | ---- | 2(2) | 5(4) |
| HYOID BONE | | | | |
| -missing, separate ossif. ctrs. | 1(1) | 1(1) | ---- | 2(2) |
| SPINAL COLUMN | | | | |
| -vertebral bodies | ---- | ---- | ---- | 1(1) |

D. DISCUSSION/CONCLUSION

a. Maternal toxicity:

Oral administration of terbuconazole during days 6-15 of gestation in the female NMRI mice produced no apparent effect upon body weights during dosing or the entire gestation period. There was no apparent changes in animal health as determined by clinical signs or mortality (see results from associated study, T5025712, on maternal toxicity).

b. Developmental toxicity:

Terbuconazole produced a non statistically significant increase in postimplantation loss in the form of late resorptions in the 100 mg/kg dose group. Statistically significant increases in runts were observed in the mid and high dose groups as compared to controls. There was a statistically significant increase in total malformations in the high dose group primarily in skull (cleft palate, micrognathia, partial dysplasia of parietal bone) and the "neural tube" (enlarged brain ventricle, asymmetry of vertebral bodies, dysplasia/abnormal spinal column) in 10 fetuses/8 litters as opposed to 1 fetus/1litter with multiple malformations. This was associated with an increase in the HDT of rudimentary ossification centers of the cranium.

c.

No significant study deficiencies were noted.

E. CLASSIFICATION: CORE MINIMUM DATA.

Maternal NOEL = 10 mg/kg/day (LDT) (based on special study submitted (T5025712)
Developmental Toxicity NOEL = 10 mg/kg/day (LDT)
Developmental Toxicity LOEL = 30 mg/kg/day

F. RISK ASSESSMENT:

Development of MOS has been determined to be unnecessary at this time.

Reviewed by: James N. Rowe, Ph.D. James N. Rowe 12/22/88
Review Section I
Toxicology Branch: Herb. Fung. Antimicroial Support (TS-769C)
Secondary Reviewer: Quang Q. Bui, Ph.D.
Review Section I, Tox. Branch: H.F.A.S. (TS-769C) Quang Bui 12/23/88

DATA EVALUATION REPORT

STUDY TYPE: Special study: maternal toxicity; Guideline Section N/A TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 408215-00

TEST MATERIAL: HWG 1608 Technical

SYNONYMS: Folicur@; terbuconazole

STUDY NUMBER: Bayer report no. 16511; T5025712; Lab. Proj. no. 97411

SPONSOR: Mobay Corporation, Agricultural Chemicals Division

TESTING FACILITY: BAYER AG, Fachbereich Toxikologie, Institute of Toxicology/Agriculture Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, FRG

TITLE OF REPORT: HWG 1608, Supplementary study of maternal toxicity to mice after oral administration

AUTHOR(S): Dr. M. Renhof and Dr. E. Karbe

REPORT ISSUED: March 9, 1988

CONCLUSIONS: It is tentatively concluded that maternal toxicity/ physiological alterations (liver enzyme induction) is demonstrated at all dose levels (10-100 mg/kg) orally administered to female mice during days 6-15 of presumed gestation. This "toxicity" was primarily demonstrated as elevations in serum AST, ALP and AP associated with increased liver weights with hepatic changes including increased mitosis, vacuolation and lipidosis. A compound-related effect upon mean corpuscular volume reflected in a reduction in hematocrit at dose levels of 20-100 mg/kg was also noted. The limited number of animals tested plus the presence in the various test groups of pregnant and non-pregnant mice makes these findings suggestive but not definitive. A maternal toxicity NOEL, based upon the reduction in hematocrit, is set at 10 mg/kg/day. This study necessitates revising the maternal NOEL in the full mouse teratology study (T5021859) to reflect the maternal toxicity NOEL.

CLASSIFICATION: ACCEPTABLE

A. MATERIALS

(A photocopy of the materials and methods section is appended).

Test compound: Purity: 97.4%
Description: gray-white, powdery crystals
Lot No: 1601c/86
Contaminants (list in CBI appendix): N/A

Vehicle(s): Distilled water with 0.5% Cremophor EL (BASF)

Test animals: Species: mice
Strain: NMRI/ORIG Kisslegg
Source: SAVO-Ivanovas GmbH, 7964 Kisslegg, FRG
Age: males, sexually mature; females, sexually mature (nulliparous)
Weight: Males, > or = 35 gms; Females, 24-40 gms

B. STUDY DESIGN

This study was designed to further assess the maternal toxicity potential of terbuconazole, when administered by gavage from gestational days 6 through 15, inclusive.

Mating:

After acclimitization for at least 6 days, 2-3 females were housed with one male for approximately 4 hours during the day. If a vaginal plug was found, this day was designated Gestation day 0.

Group Arrangement: (males were not treated)

| Test group | Dose level (mg/kg) (% conc.) | Number assigned |
|---|---|---|
| Control | 0 (0) | 10 |
| Low dose | 10 (0.2) | 10 |
| Mid 1 | 20 (0.4) | 10 |
| Mid 2 | 30 (0.6) | 10 |
| High dose | 100 (2.0) | 10 |

Dosing:

All doses were in a volume of 5 ml/kg of body weight/day prepared daily during the dosing period. The dosing solutions were analyzed for stability and homogeneity. Dosing was based on body weights adjusted daily during the treatment period and was performed each day between 8 a.m. and noon.

Observations

The animals were checked for mortality or abnormal condition daily. Body weights were determined during the treatment period and the entire gestation period. Dams were sacrificed on day 16 postcoitus. One-half of mice internal organs (selected randomly) were grossly examined and the weights of the liver, spleen, kidneys and adrenal were determined. Blood samples were obtained from 5 anesthetized mice/dose group and the following measurements made: aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, GLDH, bilirubin, creatinine, urea, total protein, triglycerides, cholesterol, hematocrit, hemoglobin, erythrocytes, mean corpuscular hemoglobin, leukocytes, MCV, MCHC, and thrombocytes. The livers were fixed in formaldehyde for histopathology.

Statistical Analysis

The following statistical analysis methods were used for clinical chemistry, hematology and liver weights:

0 t-test (method of Welch)

Statistical signficance was set at a probability error of 5%.

Compliance

- A signed Statement of No Confidentiality Claim was provided.

- A signed Statement of Compliance with OECD GLP's was provided.

- A signed Quality Assurance Statement was provided.

C. RESULTS

1. Clinical signs/mortality

Mortality

No deaths in any dose group were reported.

Clinical observations

No abnormal signs of compound-related toxicity were reported except for one dam which experienced wheezing at day 8 p.c. (LDT).

2. Body weight

The investigators supplied the following data: individual body weights for day 0, 6-15 and mean body weight gains for days 6-15. Mean body weights during dosing and gestation are presented below:

Table I: Mean body weights/ b. wt gains (grams)[a]
(pregnant animals only)

| Group: | d6 | d10 | d15 | d6-15 | # pregnant |
|---|---|---|---|---|---|
| Control | 35.2 | 38.4 | 47.2 | 12.0 | 5 |
| LDT | 34.7 | 37.3 | 45.6 | 10.9 | 7 |
| MD1 | 35.3 | 37.3 | 44.2 | 8.9 | 6 |
| MD2 | 35.4 | 39.2 | 50.2 | 14.8 | 5 |
| HDT | 33.2 | 35.0 | 41.3 | 8.2 | 5 |

[a] = data extracted from pp.61 and 70-74 of report

There was no evidence of a consistent compound-related effect in the treated dams during the dosing period.

3. Organ weights

Absolute and relative liver weights (gm, mg/gm) are presented below: (includes pregnant + nonpregnant)

| Group: | absolute | relative | # pregnant |
|---|---|---|---|
| Control | 1988.2(549.3)[a] | 49.7 | 2 |
| LDT | 2430.4(506.0) | 52.3 | 4 |
| MD1 | 2368.8(738.3) | 55.1 | 3 |
| MD2 | 2547.4(798.6) | 55.38 | 3 |
| HDT | 2379.2(342.3) | 63.25 | 3 |

[a]mean(S.D.); data extracted from p. 75

The absolute liver weights were consistently elevated in treated animals as compared to the controls. This was also reflected in the relative liver weights particularly at the HDT.

4. Clinical chemistry/hematology

Selected clinical chemistry, liver homogenate triglyceride and hematology values are presented below:

CLINICAL CHEMISTRY/LIVER HOMOGENATE (from pp.63, 65)

| Dose(mg/kg) | AST(U/L) | ALT(U/L) | AP(U/L) | CHOL(MMOL/L) | LIVER TG(UMOL/G) #P |
|---|---|---|---|---|---|
| Control | 262.7 | 46.8 | 98.8 | 1.51 | 11.61 (3) |
| (3) | (278.2)[A] | (13.7) | (58.3) | (0.20) | (0.77) |
| 10 | 534.6 | 72.2* | 61.5 | 2.21 | 10.30 (3) |
| (3) | (448.0) | (18.5) | (50.1) | (0.58) | (1.15) |
| 20 | 371.1 | 59.6 | 106.0 | 2.56** | 12.53 (3) |
| (3) | (192.2) | (15.0) | (49.7) | (0.68) | (2.27) |
| 30 | 562.3* | 67.3* | 110.0 | 2.06 | 11.21 (3) |
| (2) | (168.2) | (18.5) | ( 7.2) | (0.56) | (0.61) |
| 100 | 339.5 | 60.7 | 113.8 | 1.40 | 30.60*(5) |
| (5) | (148.1) | (13.7) | (35.9) | (0.10) | (12.57) |

HEMATOLOGY (from p. 64)

| Dose(mg/kg) | HEMATOCRIT(L/L) | MCV(fl) |
|---|---|---|
| Control(3) | 0.451(0.0125) | 54.4(0.89) |
| 10 (3) | 0.453(0.0391) | 52.6(3.21) |
| 20 (2) | 0.432(0.0251) | 50.6(3.29)* |
| 30 (2) | 0.418(0.020)*** | 52.2(1.92)* |
| 100 (5) | 0.425(0.0135)*** | 51.6(1.34)# |

[A] mean (S.D.); *, **, ***, # : $p<0.05$, $p<0.025$, $p<0.01$, $p<0.005$, respectively; ( ) = number pregnant/group of five

There was a generally consistent, often statistically significant, increase in the liver enzymes, AST and ALT, in all compound-treated groups. Non-statistically significant elevations in 20, 30 and 100 mg/kg dose groups of AP, another liver-related enzyme, were also noted. Cholesterol concentrations in the serum were statistically signficantly elevated at 20 mg/kg as compared to controls. Analysis of liver homogenate triglycerides concentrations indicated a statistically significant increase at the HDT as compared to controls.

Hematocrits were significantly lowered in the 20-100 mg/kg dose groups parallel to a significant depression in mean corpuscular volume as compared to the respective controls.

Variabilities in these clinical and hematological parameters relates to the limited number of samples analyzed as well as to the observation of considerable difference in the physiological state of the female mice (pregnancy state).

5. Gross pathology/histopathology

Upon necropsy the liver was reported as a potential target organ based upon its pale, lobular pattern as evident below:

| Finding | control | 10" | 20" | 30" | 100 mg/kg |
|---|---|---|---|---|---|
| -pale liver | 1/5 | 0/5 | 0/5 | 1/5 | 5/5* |
| -lobular pattern, liver | 0/5 | 1/5 | 0/5 | 1/5 | 3/5 |

* one animal had putty colored liver; data from p. 69

The histopathological state of treated animal livers supports the clinical chemisty findings and gross pathology (see table below). Increased mitosis was noted in the low and mid dose groups with the high dose group having a significant increase in vacuolation in all animals (mild to severe in nature) as compared to no such findings in the control livers. The frequency and severity of lipid deposition was also increased in all animals receiving terbuconazole as compared to controls with all HDT animals having moderate to severe lipidosis. These findings are indicative of disruption of the normal metabolic state of the hepatocytes.

Histopathology (data from Table 1, p. 79)

| Finding | control | 10" | 20" | 30" | 100 mg/kg |
|---|---|---|---|---|---|
| -focal necrosis | 1/5(3)* | 1/5(1) | 0/5 | 0/5 | 0/5 |
| -cellular infiltrates | 1/5(1) | 1/5(1) | 1/5(2) | 1/5(1) | 2/5(1) |
| -increased mitosis | 0/5 | 2/5(1) | 1/5(1) | 3/5(1) | 0/5 |
| -vacuoles | 0/5 | 0/5 | 0/5 | 0/5 | 5/5(2,2,3,3,4) |
| -lipidosis-ORO stain | 2/5(1) | 3/5(1) | 5/5(1,1,1,1,2) | 4/5 (1,1,2,2) | 5/5(3,3,3,3,4) |

* grade: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

D. CONCLUSIONS

Further evaluation of the maternal toxicity of terbuconazole was performed in NMRI female mice orally gavaged with 0, 10, 20, 30 and 100 mg/kg during days 6-15 of presumed gestation. No consistent alteration in body weight was evident, although the small sample size and the presence of both pregnant and nonpregnant mice makes this finding tentative. The liver was a primary target organ with 1) elevations in AST(SGOT), ALT(SGPT) and AP at all treatment doses associated with a consistent increase in absolute and relative liver weights, 2) an increase in pale, lobular appearance in HDT animals, 3) increased presence of mitosis, vacuolation and lipidosis generally extending through all animals receiving terbuconazole. A significant decrease in hematocrit values from 20-100 mg/kg was noted and was related to a diminished RBC volume. These findings tentatively support the contention of the registrant that maternal toxicity existed in pregnant dams previously tested for developmental toxicity at 10, 30 and 100 mg/kg (Study # T5021859) and in which there was no overt evidence of toxicity based upon body weights, clinical signs and lack of mortality.

Appendix 2. Mouse Dermal Developmental Toxicity Study.

Appendix 2. Mouse Dermal Developmental Toxicity Study.

GUIDELINE: 83-3

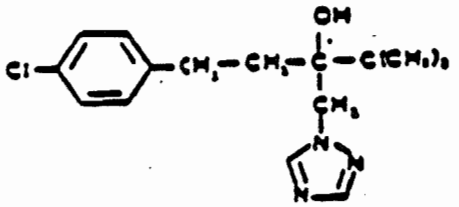
Reviewed by: Alberto Protzel, Ph.D. 4/21/92
Review Section III, Toxicology Branch II/HED (H7509C)
Secondary Review by: James N. Rowe, Ph.D. 4/21/92
Section Head, Review Section III, Toxicology Branch II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity (Dermal application)
Species: Mouse
EPA Guideline: 83-3

EPA Identification No.s: EPA MRID No. 420103-01
Caswell No. 463P
HED Project No. 2-0329
DP Barcode No. D170624
Submission No. S406118

Test Material: HWG 1608 (Technical) 98.1% a.i., Batch No. 16002/85 (Main study).



Synonyms: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

Sponsor: BAYER AG; Institut fur Toxicologie Landwirtschaft; Wuppertal 1; Federal Republic of Germany.

Study Number: 224256

Testing Facility: RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland.

Title of Report: Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application).

Author(s): H. Becker et al.

Report Issued: July 16, 1990

Conclusions:

Dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day, 6h/day, during days 6-15 of gestation in the NMRI/KFM/HAN mouse did not produce any evidence of maternal toxicity. A supplementary study (MRID 420103-01, submitted in the same volume with the present study)

with NMRI/KFM/HAN mice dosed according to the same protocol indicates a maternal toxicity dermal NOEL of 100 mg/kg/day and a maternal toxicity dermal LOEL of 300 mg/kg/day based on histological observation of dose-dependent fatty changes in periportal areas of the liver, statistically significant elevation of plasma (ALT/GPT) at the HDT, and induction of liver microsomal enzymes at the MDT and the HDT.

The fetal incidence of palatoschisis was somewhat higher at the HDT (12/285, 4.2%) than in concurrent controls (8/301, 2.7%), but it was not statistically significant. Litter incidence was 7/25 litters (28%) in both HDT and concurrent controls. Historical control incidence of palatoschisis (1 study) was 5/307 fetuses (1.6%) and 5/24 litters (20.8%).

The fetal incidence of exencephaly was somewhat higher at the HDT (2/285, 0.7%) than in concurrent controls (1/301, 0.3%), but it was not statistically significant. Litter incidence was 1/25 litters (4%) in both HDT and concurrent controls. Historical control incidence of exencephaly was 5/307 fetuses (0.3%) and 1/24 litters (4.2%).

Examination of the skeletal findings revealed statistically significant increases vs controls in the HDT fetal incidences of bipartite sternebra (11 vs 3.8%), supernumerary ribs (72 vs 48%), and non-ossification of phalanxes in the forelimbs (e.g. 12.4 vs 6.2%), in addition of up to two-fold increases in their litter incidences. These statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT. Thus, this study defines a tentative LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity.

D. Study Deficiencies:

No significant study deficiencies were noted.

E. Core Classification: Core minimum

**Maternal NOEL = 100 mg/kg/day**
**Maternal LOEL = 300/mg/kg/day**
**Developmental Toxicity NOEL = 300 mg/kg/day**
**Developmental Toxicity LOEL = 1000 mg/kg/day**

A. Materials

A copy of the "Materials and Methods" section from the report is appended.

Test Compound: Purity: 98.1% (Main study)
Description: Colorless crystals
Lot No.: 16002/85 (Main study)
Contaminants: A certificate of analysis was included.

Vehicle(s): Aqueous 4.0% (w/v) carboxymethylcellulose, CMC (Fluka AG).

Test Animal(s): Species: Mouse
Strain: NMRI KFM-HAN (Outbred, SPF quality)
Source: KFM, Kleintierfarm Madorin AG, Switzerland
Age: 8 weeks at mating
Weight: 22-38 g

B. Study Design

This study was designed to assess the effects of HWG Technical on embryonic and fetal development in the mouse when applied dermally on days 6-15 of gestation.

Mating:

Mating took place overnight, one male was placed with three females. The day in which a vaginal plug was found was designated as day 0 of gestation (day 0 post-coitum).

Group Arrangement:

Animals were randomized using a computer generated algorithm. Dose levels are shown in Table 1.

Table 1. Dose levels used in testing

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Control | 0 (Vehicle Control) | 35 (1-34) |
| Low dose (LDT) | 100 | 30 (35-64) |
| Middle dose (MDT) | 300 | 34 (65-98) |
| High dose (HDT) | 1000 | 30 (99-128) |

Dosing:

All doses were administered by the dermal route in a volume of 2.5 ml/kg of body weight/day in aqueous 4% CMC during the dosing period. The dosing solutions were applied evenly to the shaved skin of the back (approx. 10% of the body surface) once daily on days 6 through 15 of gestation. The area of application was covered with an occlusive bandage; the bandage was removed after six hours of contact. It was not stated if the skin was washed after

removal of the bandages. The dosing volume (2.5 ml/kg/day) was adjusted daily for changes in body weight.

Dosing suspensions were prepared daily. The suspensions were reportedly analyzed for concentration, homogeneity, and stability on five occasions during the dosing period and for concentration and homogeneity once during the dosing period. Samples analyzed on 12/28/88, 1/10/89, and 3/1/89 ranged from 88.1-92.0% of nominal. A sample analyzed on 2/27/89 had a range of 68.1-79.3% of nominal. Data for one analysis indicated that an HWG-1608 suspension was stable for at least 6 hours after preparation. Analytical data for all the six occasions in which analyses were reportedly done were not available for review. The four reported dates of analysis 12/28/88, 1/10/89, 2/27/89, 3/1/89 make it unclear whether the dosing was done with one or two batches of animals (i.e 12/28/88-1/10/89 and 2/27/89-3/1/89). No explanation was offered by the authors.

Table 2. Day 0 of gestation at the various dosage groups.

| Control | | LDT | | MDT | | HDT | |
|---|---|---|---|---|---|---|---|
| No.[a] Dams | Day 0 of Gestation | No. Dams | Day 0 of Gestation | No. Dams | Day 0 of Gestation | No. Dams | Day 0 of Gestation |
| 16(1) | 12/29-1/2 | 20(0) | 12/29-1/2 | 16(3) | 12/29-1/2 | 20(0) | 12/29-1/2 |
| 9(5) | 1/12-1/15 | 5(3) | 1/12-1/15 | 9(7) | 1/12-1/14 | 5(2) | 1/12-1/15 |
| 9(2) | 2/13 | 5(2) | 2/11-2/13 | 9(0) | 2/13 | 5(1) | 2/11-2/13 |

[a] Number of mated dams. Numbers in parenthesis indicate number of non-pregnant dams.

Observations:

The animals were checked for mortality and systemic symptoms twice each day of the entire study. Skin reaction was assessed by the Draize scoring system. Body weights were recorded daily from day 0 of gestation through day 18 of gestation. The dams were sacrificed at day 18 of gestation.

Examinations at sacrifice consisted of: examination of gross lesions, counting of corpora lutea, determination of the number, distribution, and viability of any fetuses present. The uteri (and contents) of all females with live fetuses were weighed to determine corrected body weight gains. If no implantation sites were evident, the uterus was placed in aqueous ammonium sulfide for visualizing possible implantation sites.

The fetuses were examined in the following manner: the fetuses were weighed, sexed and examined for external alterations. One half of the live fetuses were examined by Wilson's slicing technique for examination of the viscera and brain. The remaining fetuses were cleared in potassium hydroxide and stained

with alizarin red S for evaluation of skeletal malformations.

Historical control data were provided to allow comparison with concurrent controls.

Statistical analysis

The following statistical analysis methods were employed:

Dunnett's test (many-one t-test) was used to compare treated groups with controls if the variables followed a normal distribution; if the variables were not normally distributed, the Steel-test (many-one rank test was used. Fisher's exact test was applied if the variables could be dicotomized without loss of information.

Compliance:

A signed Statement of No Confidentiality Claim was provided.

A signed and dated Statement of compliance with EPA GLP's was provided.

A signed and dated Quality Assurance Statement was provided.

Results:

1. Maternal Toxicity

Mortality:

No deaths were observed during the course of the study.

Clinical Observations:

No abnormal clinical signs were observed. One dam in the HDT (dam #102) delivered spontaneously on day 17 of gestation (7 fetuses were found dead in the morning of day 17 of gestation) and was sacrificed: necropsy revealed 7 empty implantation sites and one dead fetus in the left uterine horn and 6 live fetuses in the right uterine horn.

Reportedly there were no local skin reactions, the Draize scores, however, were not reported.

Body Weights

There were no apparent effects on mean body weights (Table 3) or on mean body weight gains (Table 4). An instance of statistically significant ($p<0.05$) increased body weight in the LDT at 12 days (38 g vs 36 g in controls) is regarded as incidental, not dose-related, and not treatment related.

Table 3. Mean body weights (From pp. 43-50 of the Study Report).

| Test Group | Body Weights, g(s.d.) | | | | | |
|---|---|---|---|---|---|---|
| | Day 0 | Day 6[a] | Day 12 | Day 15[b] | Day 16 | Day 18[c] |
| Control | 28 (2.6) | 32 (3.1) | 36 (3.1) | 42 (3.9) | 45 (4.6) | 53 (6.3) |
| LDT | 29 (2.2) | 32 (2.5) | 38 (2.8)* | 44 (3.3) | 47 (3.7) | 56 (5.1) |
| MDT | 28 (1.7) | 31 (1.2) | 36 (2.2) | 43 (2.7) | 46 (3.0) | 56 (4.0) |
| HDT | 28 (2.7) | 32 (2.7) | 36 (3.3) | 42 (4.3) | 44 (5.0) | 53 (6.7) |

[a] First day of dosing.
[b] Last day of dosing.
[c] Day of sacrifice.
* Statistically significant at the 5% level, with respect to controls.

Table 4. Mean body weight gains (From pp. 51-55 of the Study Report)

| Test Group | Body Weight Gains, g(%) | | | |
|---|---|---|---|---|
| | Day 0-6 | Day 6-16[a] | Day 16-18 | Corrected body weight gain, days 6-18[b] |
| Control | 4 (+14.3) | 13 (+40.6) | 8 (+17.8) | 3.5 (+11.5) |
| LDT | 3 (+10.3) | 15 (+46.9) | 9 (+19.1) | 3.5 (+11.0) |
| MDT | 3 (+10.7) | 15 (+48.4) | 10 (+21.7) | 4.1 (+13.1) |
| HDT | 4 (+14.3) | 12 (+37.5) | 9 (+20.5) | 3.9 (+12.6) |

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 18 of gestation.
[b] Corrected body weight: (body weight at sacrifice) - (b.w. on day 6) - (weight of gravid uterus at cesarean section).

Food Consumption

There were no apparent effects on food consumption (Table 5). An instance of statistically significant ($p<0.05$) increased food consumption in the LDT at days 16-18 (12.5 g vs 11.5 g in controls) is regarded as incidental, not dose-dependent, and not treatment related.

Table 5. Mean Food Consumption (From pp. 36-41 of the Study Report).

| Test Group | Food Consumption, g (% of control) at Days: | | | | |
|---|---|---|---|---|---|
| | 0-6 | 6-11[a] | 11-16 | 6-16[b] | 16-18 |
| Control | 6.4 | 7.1 | 8.6 | 7.9 | 11.5 |
| LDT | 6.4 (+0.0) | 7.3 (+2.8) | 8.8 (+2.3) | 8.1 (+2.5) | 12.5 (+8.7)* |
| MDT | 6.5 (+1.6) | 7.3 (+2.8) | 8.9 (+3.5) | 8.1 (+2.5) | 11.9 (+3.5) |
| HDT | 6.4 (+0.0) | 7.0 (-1.4) | 8.8 (+2.3) | 7.9 (+0.0) | 12.4 (+7.8) |

[a] Day 6 = first day of dosing.
[b] Day 16 = last day of dosing.
[c] Day 18 = day of sacrifice.
* Statistically significant at the 5% level with respect to controls.

Gross Pathological Observations

No abnormal findings were observed.

Cesarean Section Observations

Pregnancy rates ranged from 76.4% in controls and the MDT to 90% in the HDT (Table. 6). No treatment related effects were reported for the total and average (i.e. per dam) number of corpora lutea, implantations, resorptions (early and late), mean number of dead and live fetuses, fetal weights, and sex ratio.

Although the number of total and early resorptions in the treated mice was not significantly different from controls, the number of affected litters at the LDT (14, $p<0.01$) and the MDT (13, $p<0.05$) was significantly higher than in controls (5 affected). Although the percent of post-implantation loss was somewhat elevated at the LDT (8.0%) and the MDT (6.4%) vs controls (5.0%), the effect was not statistically significant, the number of affected litters at the LDT (19, $p<0.01$) and the MDT (16, $p<0.05$) was significantly higher than in controls (8 affected).

Table 6: Cesarean Section Observations for Dams with Live Fetuses (From pp. 25, 56-57, 58-61, 70-97 and pp. 99-102 of the Study Report).

| Parameter | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #Animals Assigned | 34 | 30 | 34 | 30 |
| #Animals Mated/Inseminated | 34 | 30 | 34 | 30 |
| Pregnancy Rate (%) | 26(76.4) | 25(83.3) | 26(76.4) | 27(90) |
| Dams with Live Fetuses | 25[1] | 25 | 24[2] | 25[3] |
| Maternal Wastage | | | | |
| #Died | 0 | 0 | 0 | 0 |
| #Died/pregnant | 0 | 0 | 0 | 0 |
| #Non pregnant | 8 | 5 | 8 | 3 |
| #Aborted | 0 | 0 | 0 | 0 |
| #Premature Delivery | 0 | 0 | 0 | 1 |
| Total Corpora Lutea | 359 | 386 | 381 | 342 |
| Corpora Lutea/Dam | 14.4 | 13.4 | 15.90 | 13.7 |
| Preimplantation Loss [Tot(%)] | 42(11.7) | 25(6.5) | 21(5.5) | 39(11.4) |
| Mean (per dam) | 1.7 | 1.0 | 0.9 | 1.6 |
| # Dams affected | 20 | 14 | 14 | 17 |
| Total Implantations | 317 | 361 | 360 | 303 |
| Implantations/Dam | 12.7 | 14.4 | 15.0 | 12.1 |
| Postimplantation Loss[Tot(%)] | 16(5.0) | 29(8.0) | 23(6.4) | 18(5.9) |
| Mean (per dam) | 0.6 | 1.2* | 1.0 | 0.7 |
| # Dams affected | 8 | 19** | 16* | 12 |
| Total Live Fetuses | 301 | 332 | 337 | 285 |
| Live Fetuses/Dam[4] | 12.04 | 13.3 | 14.0 | 11.4 |
| Total Resorptions | 16 | 29 | 23 | 18 |
| Early ("Embryonic") | 12 | 20 | 16 | 14 |
| No. Dams affected | 5 | 14** | 13** | 9 |
| Late ("Fetal") | 4 | 9 | 7 | 4 |
| No. Dams affected | 3 | 7 | 7 | 3 |
| Resorptions/Dam | 0.64 | 1.2 | 0.96 | 0.72 |
| Total Dead Fetuses | 0 | 0 | 0 | 0 |
| Dead Fetuses/Dam | 0 | 0 | 0 | 0 |
| Mean Fetal Weight (gm) | 1.2 | 1.2 | 1.1 | 1.2 |
| Sex Ratio (% Males/litter) | 51.2 | 50.0 | 55.2 | 51.9 |

[1] One female (No. 16) had two implantation sites only).
[2] Two females (Nos. 69 and 80), had 6 and 9 implantation sites only.
[3] One female (No. 108) had 2 embryonic resorptions only; another female (No. 102) delivered prematurely on day 17 of gestation and was necropsied.
[4] Counting only dams with live fetuses (e.g. 25 in controls).

2. Developmental Toxicity

External examinations

As shown in Table 6, the incidence of palatoschisis at the HDT was 12/285 fetuses (4.2%) vs. 8/301 fetuses (2.7%) in controls. On the other hand, the litter incidence of palatoschisis (7/25, 28%) was identical in controls and in HDT mice. Although the fetal incidence of palatoschisis may be somewhat higher in the HDT, the effect was not statistically significant. The incidence of palatoschisis in historical controls (1 study, 5/87-7/87, with NMRI/HAN/ outbred SPF quality, Appendix 2) was 5/307 fetuses (1.6%) and 5/24 litters (20.8%). It is noted that in this study the incidence of palatoschisis in controls and at the HDT was somewhat higher than in the historical controls.

Exencephaly was observed in 2/285 fetuses (0.7%) at the HDT and in 1/301 (0.3%) fetuses in concurrent controls. The effect was not statistically significant. Litter incidences at the HDT and concurrent controls were identical 1/25 (4%). Historical controls were 0.3% fetuses and 4.2% litters.

One dam in the HDT (dam #102) delivered spontaneously on day 17 of gestation (7 fetuses were found dead in the morning of day 17 of gestation) and was sacrificed: necropsy revealed 7 empty implantation sites and one dead fetus in the left uterine horn and 6 live fetuses in the right uterine horn. No data on these fetuses from dam #102 were included.

Table 6. External examinations in cesarean-delivered pups. Data from pp. 62-63 and pp. 78-97 of the Study Report.

| Observations | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups (litters) examined | 301(25) | 332(25) | 337(24) | 285(25) |
| # pups (litters) affected | 9(8) | 10(8) | 6(6) | 15(9) |
| Finding: pups(litters) | | | | |
| Palatoschisis | 8(7) | 8(6) | 4(4) | 12(7) |
| Tail cranial-bended | 1(1) | - | 1(1) | - |
| Exencephaly | 1(1) | 1(1) | - | 2(1) |
| Hind leg malposition: | | | | |
| Right leg | 1(1) | - | 1(1) | - |
| Left leg | - | 1(1) | - | 2(2) |

Visceral Examinations

Table 7 summarizes the visceral examination data, none of the findings reached statistical significance.

Table 7. Visceral examinations in cesarean-delivered pups (Wilson technique). Data from p. 64 of the Study Report.

| Observations | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups (litters) examined | 142(25) | 161(25) | 162(24) | 140(25) |
| # pups (litters) affected | 5(4) | 9(7) | 3(3) | 12(7) |
| Finding: pups(litters) | | | | |
| Palatoschisis | 5(4) | 8(6) | 3(3) | 11(7) |
| Exencephaly | - | 1(1) | - | 2(2) |

Skeletal Examinations

Skeletal findings are presented below in Table 8. At the HDT there was statistical significance vs control in the fetal incidence of several skeletal variations, in addition to increases of up to 2-fold in litter incidences:

- Bipartite sternebra 5: 16/145 fetuses (11.0%) vs 6/159 (3.8%) [($p \leq 0.05$)], and 10/25 litters (40%) vs 5/25 (20%).
- Supernumerary ribs, one, right: 105/145 fetuses (72%) vs 76/159 (48%) [($p \leq 0.01$)], and 25/25 litters (100%) vs 22/25 (88%).
- Left forelimb, non-ossified distal phalanx digit 2: 18/145 (12.4%) vs 10/159 (6.2%) [($p \leq 0.05$)], and 11/25 litters (44%) vs 8/25 (32%).
- Right forelimb, non-ossified distal phalanx, digit 4: 19/145 fetuses (13%) vs 9/159 (9.7%) [($p \leq 0.05$)], and 10/25 litters (40%) vs 7/25 (28%).

Examination of Table 8 also indicates that, in addition, there were statistically significant decreases at the HDT and/or LDT in the fetal incidence of non-ossified phalanxes of the hindlimbs. These effect, however, did not produce any marked effects in litter incidences.

Table 8. Summary of skeletal observations in cesarean-delivered pups. Data from pp. 65-69 and 231-443 of the Study Report.

| Observations | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups (litters) examined | 159(25) | 171(25) | 175(24) | 145(25) |
| SKULL | | | | |
| Part of cranium missing, (externally, as exencephaly) | 1(1)[a] | - | - | - |
| CERVICAL VERTEBRAE | | | | |
| Vertebra 2 (Non-ossified) | 19(9) | 10*(6) | 20(8) | 14(8) |
| STERNUM | | | | |
| Assymetric sternebrae (2-5) or (4 and 5) | 3(3) | 1(1) | 1(1) | - |
| Assymetric and bipartite sternebrae (2-5) | - | - | - | 1(1) |
| Assymetric sternebra (3 and 4) | - | - | - | 1(1) |
| Incompletely ossified Sternebra 5 | 128(25) | 134(25) | 156*(24) | 108(24) |
| Bipartite sternebra 5 | 6(5) | 9(7) | 2(1) | 16*(10) |
| RIBS | | | | |
| Supernumerary "flying rib" (No. 14), left | - | - | 1(1) | - |
| Supernumerary, one, left | 92(23) | 106(25) | 105(22) | 107*(25) |
| Supernumerary, one, right | 76(22) | 100*(25) | 91(22) | 105**(25) |
| LEFT FORELIMB (Non-ossified) | | | | |
| Digit 2, medial phalanx | 139(25) | 149(25) | 150(24) | 122(23) |
| Digit 2, distal phalanx | 10(8) | 9(7) | 3*(3) | 18*(11) |
| Digit 4, distal phalanx | 10(8) | 9(6) | 3*(3) | 17(10) |
| RIGHT FORELIMB (Non-ossified) | | | | |
| Digit 2, medial phalanx | 137(25) | 143(25) | 145(24) | 122(23) |
| Digit 2, distal phalanx | 9(7) | 9(7) | 5(4) | 16(8) |
| Digit 4, distal phalanx | 9(7) | 11(7) | 5(4) | 19*(10) |
| LEFT HINDLIMB (Non-ossified) | | | | |
| Toe 5, proximal phalanx | 34(10) | 17**(9) | 29(11) | 14**(8) |
| Toe 5, distal phalanx | 32(10) | 16**(7) | 19*(9) | 25(13) |
| RIGHT HINDLIMB (Non-ossified) | | | | |
| Toe 5, proximal phalanx | 32(9) | 16*(9) | 31(13) | 15*(9) |
| Toe 5, distal phalanx | 30(10) | 15*(7) | 19(10) | 25(13) |

[a] Fetal(litter) incidence.
* Significant at the 5% level. ** Significant at the 1% level.

Discussion/Conclusions

a. Maternal Toxicity:

Dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation in the NMRI/KFM/HAN mouse did not produce any evidence of maternal toxicity, as determined by mortality, clinical observations, mean body weights, mean body weight gains (corrected and uncorrected), food consumption and gross pathology findings. Thus, based on the data presented in the Main Part of this study the maternal toxicity NOEL and LOEL remain to be determined.

A supplementary study (MRID 420103-01, submitted in the same volume with the present study) with NMRI/KFM/HAN mice dermally dosed with aqueous 4% CMC tebuconazole at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation provides tentative values for the maternal NOEL and LOEL. This supplementary study indicates a dermal NOEL of 100 mg/kg/day and a dermal LOEL of 300 mg/kg/day based on histological observation of dose-dependent fatty changes in periportal areas of the liver, statistically significant elevation of plasma (ALT/GPT) at the HDT, and induction of liver microsomal enzymes at the MDT and the HDT.

It is noted that in a DER (dated 12/22/1988) of a supplementary study of maternal toxicity to NMRI/ORIG Kisslegg mice after oral administration of tebuconazole (10, 20, 30, and 100 mg/kg, MRID 408215-01, Addendum 1) in 0.5% aqueous Cremophor EL, the LOEL was set at 20 mg/kg/day based on hematological effects and the NOEL was set at 10 mg/kg/day. In the present study with NMRI/KFM/HAN mice, the LOEL and NOEL were 300 and 100 mg/kg/day, respectively. These values, higher than those obtained by the oral route, are suggestive of a decreased bioavailability of tebuconazole when administered dermally in an aqueous medium.

b. Developmental Toxicity:

Although the number of total and early resorptions in the treated mice was not significantly different from controls, the number of affected litters at the LDT (14, $p<0.01$) and the MDT (13, $p<0.05$) was significantly higher than in controls (5 affected). Although the percent of post-implantation loss was somewhat elevated at the LDT (8.0%) and the MDT (6.4%) vs controls (5.0%), the effect was not statistically significant, the number of affected litters at the LDT (19, $p<0.01$) and the MDT (16, $p<0.05$) was significantly higher than in controls (8 affected).

Although the fetal incidence of palatoschisis was somewhat higher at the HDT (12/285, 4.2%) than in concurrent controls (8/301, 2.7%), it was not statistically significant. Litter incidence was 7/25 litters (28%) in both HDT and concurrent controls. In the present study the incidence of palatoschisis in controls and in the HDT was somewhat higher than in the historical controls [Appendix 2], in which the incidence of palatoschisis was 5/307 fetuses (1.6%) and 5/24 litters (20.8%).

Although the fetal incidence of exencephaly was somewhat higher at the HDT (2/285, 0.7%) than in concurrent controls (1/301, 0.3%), it was not statistically significant. Litter incidence was 1/25 litters (4%) in both HDT and concurrent controls. In the present study the incidence of exencephaly in the HDT was somewhat higher than in the historical controls, [Appendix 2], in which the incidence of exencephaly was 5/307 fetuses (0.3%) and 1/24 litters (4.2%), [Appendix 2].

Examination of the skeletal findings revealed statistically significant increases in the fetal incidences of bipartite sternebra, supernumerary ribs, and non-ossification of phalanxes in the forelimbs, in addition of up to two-fold increases in their litter incidences:

- Bipartite sternebra 5: 11.0% fetuses (HDT) vs 3.8% (controls) [($p \leq 0.05$)] and 40% litters (HDT) vs 20% (controls).
- Supernumerary ribs, one, right: 72% fetuses (HDT) vs 48% (controls [($p \leq 0.01$)], and 100 % litters (HDT) vs 88% (controls).
- Left forelimb, non-ossified distal phalanx digit 2: 12.4% fetuses (HDT) vs 6.2% (controls) [($p \leq 0.05$)], and 44% litters (HDT) vs 32% (controls).
- Right forelimb, non-ossified distal phalanx, digit 4: 13% fetuses (HDT) vs 9.7% (controls) [($p \leq 0.05$)], and 40% litters (HDT) vs 28% (controls).

The above statistically significant increases in fetal incidences of skeletal variations, coupled to marked increases in their litter incidences (e.g. bipartite sternebrae 20% controls up to 40% at the HDT) are suggestive of an incipient treatment-related effect at the HDT. Thus, this study defines a tentative LOEL of 1000 mg/kg/day and a NOEL of 300 mg/day for developmental toxicity.

D. Study Deficiencies:

No significant study deficiencies were noted.

E. Core Classification: Core minimum data.

Maternal NOEL = 100 mg/kg/day
Maternal LOEL = 300/mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day
Developmental Toxicity LOEL = 1000 mg/kg/day

F. Risk Assessment:

Lowest-estimates of the Margin of Exposure (MOE) values for tebuconazole-containing pesticides have been determined using an oral mouse NOEL of 10 mg/kg/day [EPA/OPP/HED Memorandum from A. Protzel to B. Chambliss/S. Lewis, dated 9/6/1991]. The lowest-estimates of the MOE values for Elite 45-DF range from 8-50 (airblast applicators) and from 233-2326 (mixer/loaders). The lowest-estimates of the MOE values for Folicur 3.6 F range from 11-83 (groundboom applicators) ands from 36-288 (mixer/loaders). The MOE for aerial applicators of Folicur 3.6 is at least 20,000, under the conditions specified in the EUP application.

To assess the toxicologic significance of the above MOE values (using mouse oral data) it must be considered that rat dermal absorption paramenters were used in their estimation. The use of dermal absorption parameters obtained following application of the ai in ethanol to rats, constitutes a worst-case scenario for dermal absorption. Administration of the ai as a suspension in water would possibly result in very limited dermal penetration, leading to increased MOE estimates for the formulations.

Further consideration of the significance of the above MOE values and of the developmental toxicity potential of tebuconazole awaits consideration in a future HED developmental toxicity Peer Review.

Page_____ is not included in this copy.

Pages 79 through 89 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Appendix 3. Mouse Dermal Maternal Toxicity Supplementary Study.

GUIDELINE: 83-3

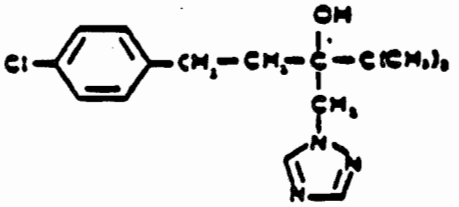
Reviewed by: Alberto Protzel, Ph.D. 4/21/92
Review Section III, Toxicology Branch II/HED (H7509C)
Secondary Review by: James N. Rowe, Ph.D. 4/21/92
Section Head, Review Section III, Toxicology Branch II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Supplementary Study: Maternal Toxicity (Dermal application)
Species: Mouse
EPA Guideline: N/A

EPA Identification Nos: EPA MRID No. 420103-01 (Supplementary Study)
Caswell No. 463P
HED Project No. 2-0329
DP Barcode No. D170624
Submission No. S406118

Test Material: HWG 1608 (Technical) 96.0% a.i., Batch No. 816896061 (Supplementary study).



Synonyms: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol.

Sponsor: BAYER AG; Institut fur Toxicologie Landwirtschaft; Wuppertal 1; Federal Republic of Germany.

Study Number: 224256

Testing Facility: RCC, Research and Consulting Company AG. P.O. Box CH 4452. Itingen/Switzerland.

Title of Report: Supplementary study to: "Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application)". This supplementary study was imbedded in the main study, it was not presented as a separate document.

Author(s): H. Becker et al.

Report Issued: Date unspecified. Date of last necropsy: August 9, 1989.

Conclusions: In this supplementary study with NMRI/KFM/HAN mice, dermal application of tebuconazole followed the same protocol as in the main study (tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days

6-15 of gestation). It is tentatively concluded that maternal toxicity /physiological alterations occurred at the MDT and the HDT. Liver Microsomal enzymes (cytochrome P-450, N- and O-demethylase) were significantly elevated (37-100%, $p \leq 0.01$) at the MDT and the HDT. Periportal fatty deposition in the liver was observed at at the MDT and the HDT. Alanine aminotransferase activity in plasma (ALT/GPT) increased in dose-dependent fashion (up to 37% at the HDT) and reached statistical significance at the HDT. All of these changes are consistent with a toxic effect on liver at the MDT. A dermal maternal toxicity LOEL of 300 mg/kg/day is set based on the induction of microsomal enzymes and periportal fatty deposition in liver. The maternal toxicity NOEL is set at 100 mg/kg/day.

Core Classification: ACCEPTABLE.

A. Materials

A copy of the "Materials and Methods" section from the report is appended.

Test Compound: Purity: 96.0 %
Description: Colorless crystals
Lot No.: 816896061
Contaminants: A certificate of analysis was included.

Vehicle(s): Aqueous 4.0% (w/v) carboxymethylcellulose, CMC (Fluka AG).

Test Animal(s): Species: Mouse
Strain: NMRI KFM-HAN (Outbred, SPF quality)
Source: KFM, Kleintierfarm Madorin AG, Switzerland
Age: 8 weeks at mating
Weight: 22-38 g

B. Study Design

Due to the absence of maternal toxic effects in the main study, a supplementary study was initiated to determine the maternal toxic dose level by histological examination or clinical laboratory examination of the treated animals. In this study test material was applied dermally to the mice on days 6-15 of gestation.

Mating:

No details were given. In the main study, mating took place overnight, one male was placed with three females. The day in which a vaginal plug was found was designated as day 0 of gestation (day 0 post-coitum).

Group Arrangement:

Details of animal randomization were not given. In the main study, animals were randomized using a computer generated algorithm. The animals were divided into two series: Series A (for histological examination) and Series B (for clinical laboratory investigation). Dose Levels were are shown in Table 1.

Table 1. Dose levels used in testing

| Test Group | Dose Level (mg/kg) | Number Assigned | |
|---|---|---|---|
| | | Series A[a] | Series B |
| Control | 0 (Vehicle Control) | 10 (1-10) | 10 (41-50) |
| Low dose (LDT) | 100 | 10 (11-20) | 10 (51-60) |
| Middle dose (MDT) | 300 | 10 (21-30) | 10 (61-70) |
| High dose (HDT) | 1000 | 10 (31-40) | 10 (71-80) |

[a] Series A (for histological examination) and Series B (for clinical laboratory investigation).

Dosing:

Dosing was done as described for the main study. All doses were administered by the dermal route in a volume of 2.5 ml/kg of body weight/day in aqueous 4% CMC during the dosing period. The dosing solutions were applied evenly to the shaved skin of the back (approx. 10% of the body surface) once daily on days 6 through 15 of gestation. The area of application was covered with an occlusive bandage; the bandage was removed after six hours of contact. It was not stated if the skin was washed after removal of the bandages. The dosing volume (2.5 ml/kg/day) was adjusted daily for changes in body weight.

Dosing suspensions were prepared daily. The suspensions were reportedly analyzed for concentration, homogeneity, and stability. Results for one analysis indicated 84.9% and 90.1% of target for the LDT and the MDT, respectively, and 74.5% of target for the HDT.

Observations:

Frequency of checking for mortality and systemic symptoms was not specified; presumably it was done at least once daily (based on daily clinical observations for one dam). Body weights were recorded daily from day 0 of gestation through day 16 of gestation. The dams were sacrificed at day 16 of gestation.

Examinations at sacrifice consisted of:

- Series A: Gross necropsy, examination of pregnancy status, and weighing of the liver and adrenals, followed by fixing and histopathology examination.
- Series B: Blood sampling prior to necropsy, gross necropsy, examination of pregnancy status, and removal of liver for in vitro assay of microsomal enzymes.

Examinations included recording of the number of living embryos, dead embryos (early and late stage), and total number of implantations.

Statistical analysis

The following statistical analysis methods were employed:

Dunnett's test (many-one t-test) was used to compare treated groups with controls if the variables followed a normal distribution; if the variables were not normally distributed, the Steel-test (many-one rank test was used. Fisher's exact test was applied if the variables could be dicotomized without loss of information.

Compliance:

Statements of EPA GLP compliance and Quality Assurance, clearly pertained to the Main Study, it is assumed (though unclear) that these statements apply also to the Supplementary Study, which was imbedded in the Main Study.

C. Results:

Mortality:

No deaths were observed during the course of the study.

Clinical Observations:

No abnormal clinical signs were observed in Controls, MDT and HDT mice. One dam in the LDT had vaginal bleeding on days 13-14 of gestation. No other signs were observed. No local skin reaction was observed at any dose level.

Body Weights

There were no apparent effects on mean body weights (Table 2) or on mean body weight gains (Table 3).

Table 2. Mean body weights (From pp. 165-168 and 181-184 of the Study Rept.)

| Test Group | Body Weights, g | | | | | |
|---|---|---|---|---|---|---|
| | Series A | | | Series B | | |
| | Day 6[a] | Day 11 | Day 16[b] | Day 6 | Day 11 | Day 16 |
| Control | 31 | 33 | 44 | 31 | 33 | 43 |
| LDT | 30 | 33 | 44 | 30 | 33 | 43 |
| MDT | 30 | 32 | 43 | 31 | 33 | 42 |
| HDT | 32 | 35 | 47 | 30 | 32 | 42 |

[a] First day of dosing.
[b] Day of sacrifice. Last day of dosing was day 15.

Table 4. Mean body weight gains (From pp. 169 and 185 of the Study Report).

| Test Group | Mean Body Weight Gains, g(%) | | | |
|---|---|---|---|---|
| | Series A | | Series B | |
| | Day 6-11[a] | Day 6-16 | Day 6-11 | Day 6-16 |
| Control | 2 (+6.5) | 13 (+41.9) | 2 (+6.5) | 12 (+38.7) |
| LDT | 3 (+10.0) | 14 (+46.7) | 3 (+10.0) | 13 (+43.3) |
| MDT | 2 (+6.7) | 13 (+43.3) | 2 (+6.5) | 11 (+35.5) |
| HDT | 3 (+9.4) | 15 (+46.9) | 2 (+6.7) | 12 (+40.0) |

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.

Food Consumption

There were no apparent effects on food consumption (Table 4).

Table 4. Mean body food consumption (From pp. 163 and 179 of the Study Report).

| Test Group | Mean food consumption, g/animal/day (% vs control) | | | |
|---|---|---|---|---|
| | Series A | | Series B | |
| | Day 6-11[a] | Day 6-16 | Day 6-11 | Day 6-16 |
| Control | 6.2 | 7.3 | 7.1 | 8.2 |
| LDT | 6.5 (+4.8) | 7.8 (+6.8) | 7.2 (+1.4) | 8.6 (+4.9) |
| MDT | 6.4 (+3.2) | 7.5 (+2.7) | 7.6 (+7.0) | 8.8 (+7.3) |
| HDT | 6.8 (+9.7) | 8.2 (+12.3) | 7.5 (+5.6) | 8.4 (+2.4) |

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.

Reproduction Values.
As summarized in Table 5, no significant differences among groups were found in No. of pregnancies, No. of dead or living embryos/dam, and the total number of implantations/dam.

Necropsy and Organ Weights.
No significant effects were observed for absolute or relative liver weights between treated groups and controls. The mean absolute weights for the adrenals were significantly reduced vs controls in all treated groups; the relative weights decreased in a dose-dependent fashion and reached statistical significance at the HDT.

Table 5. Reproduction values (From pp. 171-172 and 194-195 of the Study Report).

| Test Group | Reproduction values | | | | | |
|---|---|---|---|---|---|---|
| | Total animals | No. pregnant | No. living embryos / dam | No. Dead/dam • embryos | | Total No. implantations/ dam |
| | | | | Early | Late | |
| Series A: | | | | | | |
| Controls | 10 | 9 | 12.4 | 0.3 | 0.1 | 12.9 |
| LDT | 10 | 8 | 11.3 | 1.3 | 0.3 | 12.8 |
| MDT | 10 | 9 | 11.6 | 0.4 | 0 | 12.0 |
| HDT | 10 | 10 | 13.9 | 0.6 | 0 | 14.5 |
| Series B: | | | | | | |
| Controls | 10 | -[b] | 11.9 | 0.2 | 0.6 | 12.7 |
| LDT | 10 | 8 | 12.8 | 0.8 | 0.4 | 13.9 |
| MDT | 10 | 8 | 9.8 | 0.8 | 1.3 | 11.8 |
| HDT | 10 | 7 | 10.6 | 0.6 | 0.1 | 11.9 |

[a] Dosing was done on days 6 through 15 gestation; the animals were sacrificed on day 16 of gestation.
[b] One dam (#43) was found dead in the morning of day 7 after mating, it was too early to determine pregnancy status. If dam #43 was not pregnant the total number of pregnancies is 9.

Table 6. Absolute and relative organ weights in treated dams (From pp. 188-193 of the Study Report)

| | Mean absolute and relative organ weights | | | | |
|---|---|---|---|---|---|
| | Body weight (g) | Liver | | Adrenals | |
| | | Absolute (g) | Relative (%) | Absolute (g) | Relative (%) |
| Controls | 42.6 | 2.39 | 5.60 | 0.017 | 0.040 |
| LDT | 39.7 | 2.25 | 5.63 | 0.012* | 0.033 |
| MDT | 41.9 | 2.38 | 5.67 | 0.011** | 0.029 |
| HDT | 47.4 | 2.73 | 5.75 | 0.012* | 0.025* |

Plasma and liver microsomal enzyme activities

As summarized in Table 7, there was a slight dose-dependent increase in the activities of AST (GOT) and ALT (GPT) in plasma (up to 37% at the HDT); this increase reached statistical significance only for ALT at the HDT. Glutamate dehydrogenase, although increased with respect to controls at all treatment groups, did not reached statistical significance vs controls at any level. Liver microsomal enzyme activities (cytochrome P-450, N- and O-demethylase) were significantly ($p \leq 0.01$) elevated (37-100%) at the MDT and the HDT. These effects on microsomal enzymes are consistent with the known effects of tebuconazole as a microsomal enzyme inducer.

Table 7. Mean plasma and liver microsomal enzyme activities of treated dams (from pp 154-158 of the Study Report).

| Finding | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| Plasma Activities: | | | | |
| Aspartate Aminotransferase (AST/GOT) µkat/l | 1.72 | 2.25 | 2.28 | 2.36 |
| Alanine Aminotransferase (ALT/GPT) µkat/l | 0.80 | 0.88 | 0.96 | 1.10* |
| Glutamate dehydrogenase (GLDH) µkat/l | 220.5 | 277.8 | 476.2 | 407.9 |
| Alkaline phosphatase (ALP) µkat/l | 1.99 | 2.02 | 2.67 | 1.99 |
| Microsomal Activities: | | | | |
| Cytochrome P-450 (nmol/g) | 30.0 | 45.1 | 74.2** | 73.6** |
| N-Demethylase (nmol/min/g) | 331.0 | 394.5 | 691.9** | 640.5** |
| O-Demethylase (nmol/min/g) | 32.27 | 31.40 | 43.78** | 41.09** |

* $p \leq 0.05$; ** $p \leq 0.01$.

As shown in Table 8, a dose dependent increase in the incidence and severity of fatty changes (stainable lipid deposition) was observed in liver. In particular, these fatty areas were limited to single cells in control and LDT mice and became extended to the periportal areas at the MDT and HDT. The severity of deposition increased in going from MDT (grades 1-2) to HDT (grades 1-3). No other apparently treatment-related effects were observed in liver or adrenals.

Table 8. Microscopic findings in treated dams (From pp 113-147 of the Study Report)

| Finding | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| Liver | | | | |
| Number Examined: | 10 | 10 | 10 | 10 |
| Fatty changes | | | | |
| Periportal (Total) | 0 | 0 | 8 | 10 |
| Grade 1 | 0 | 0 | 7 | 4 |
| Grade 2 | 0 | 0 | 1 | 5 |
| Grade 3 | 0 | 0 | 0 | 1 |
| Single cell | 10 | 10 | 2 | 0 |
| Single cell necrosis | 2 | 1 | 3 | 2 |
| Hepatocytic vacuolation | 1 | 1 | 1 | 1 |
| Adrenals | | | | |
| Number Examined: | 10 | 10 | 10 | 10 |
| Lipogenic pigment | 9 | 8 | 9 | 10 |
| Cortical vacuolization | 2 | 0 | 2 | 2 |
| A-cell hyperplasia | 6 | 6 | 6 | 9 |
| Monuclear infiltrate | 0 | 0 | 1 | 1 |

Discussion/Conclusions

Due to the absence of maternal toxic effects in the main study (dermal administration of tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation in the NMRI/KFM/HAN mouse), a supplementary study was initiated to determine the maternal toxic dose level.

In this supplementary study also with NMRI/KFM/HAN mice, dermal application of tebuconazole followed the same protocol as in the main study (tebuconazole in aqueous 4% CMC at 0, 100, 300, and 1000 mg/kg/day during days 6-15 of gestation). The animals were sacrificed on day 16 of gestation for histological examination of liver and adrenals and assay of plasma and liver microsomal enzyme activities.

No significant effects on mortality, body weight gains, food consumption, and reproduction values were observed on treated animals vs controls. No effect was observed on absolute or relative liver weights; relative adrenal weights decreased in a dose-dependent fashion and reached statistical significance at the HDT.

Histopathology and enzyme activity studies revealed some effects on the liver at the HDT. Liver microsomal enzymes (cytochrome P-450, N- and O-demethylase) were significantly elevated (37-100%, $p \leq 0.01$) at the MDT and the HDT. These effects on microsomal enzymes are consistent with the microsomal enzyme-inducing property of tebuconazole. Alanine aminotransferase activity in plasma (ALT/GPT) increased in a dose-dependent fashion (up to 37% at the HDT) and reached statistical significance at the HDT. Histopathology of the liver revealed a dose-dependent increase in the incidence and severity of fatty changes (stainable fatty deposition) in the liver. These changes consisted of transition from stainable fat in individual cells (controls and LDT) to stainable fat in periportal areas of increasing severity at the MDT (up to degree 2) and the HDT (up to degree 3).

Together, the above evidence supports the idea that a pharmacologic/toxic effect was reached at the MDT and HDT.

Page_____ is not included in this copy.

Pages 100 through 101 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Appendix 4. Rat Oral Developmental Toxicity Study.

Appendix 4. Rat Oral Developmental Toxicity Study.

Reviewed by: James N. Rowe, Ph.D. James N. Rowe 11/14/88
Review Section I
Toxicology Branch: Herb. Fung. Antimicrobial Support (TS-769C)
Secondary Reviewer: Quang Q. Bui, Ph.D. Quang Q Bui 12/9/88
Review Section I, Tox. Branch: H.F.A.S. (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity Guideline Section 83-3 TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 407009-43

TEST MATERIAL: HWG 1608 Technical

SYNONYMS: Folicur@; terbuconazole

STUDY NUMBER: 074057; Lab. Proj. ID No. 96756; BAYER: T 9023301

SPONSOR: BAYER AG, Institut fuer Toxikologie Landwirtschaft, Fachbereich Toxikologie, D-5600 Wuppertal, FRG

TESTING FACILITY: RCC, Research & Consulting Company AG, and RCC, Umweltchemie AG, CH 4452 Itingen/Switzerland

TITLE OF REPORT: Embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rat

AUTHOR(S): H. Becker (study director)

REPORT ISSUED: April 28, 1988

CONCLUSIONS:

Oral administration of terbuconazole at 0, 30, 60 and 120 mg/kg/day during days 6-15 of gestation in Wistar rats produced slight maternal toxicity as evidenced by a small depression in mean body weight associated with depressed food consumption. Mean liver weights and liver to body weight ratios were statistically significantly elevated in the mid and high dose groups. The maternal NOEL is set at 30 mg/kg/day.

Developmental toxicity was evidenced at both the mid and high dose groups by delays in ossification of thoracic, cervical and sacral vertebrae, the sternum and fore- and hind limbs along with an increase in supernumerary ribs. Frank malformations were observed in two fetuses of two high dose dams as missing tail, agnatha, microstomia and anophthalmia. The developmental NOEL is set at 30 mg/kg/day.

CLASSIFICATION: CORE MINIMUM

## A. MATERIALS

(A photocopy of the materials and methods section is appended).

Test compound: Purity: 98.3%
Description: colorless crystals
Lot No: 16002/85
Contaminants (list in CBI appendix): N/A

Vehicle(s): Distilled water with 0.5% Cremophor EL (BASF)

Test animals: Species: rat
Strain: Wistar/HAN (Kfm: WIST, Outbred, SPF quality)
Source: KFM, Kleintierfarm Madoerin AG, CH 4414 Fuellinsdorf/Switzerland
Age: 12 weeks, minimum (at pairing)
Weight: 180-235 gms

## B. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of terbuconazole, when administered by gavage from gestational days 6 through 15, inclusive.

Mating:

After acclimitization for 7 days, females were housed with males (1:1) overnight until either the daily vaginal smear was sperm-positive or a copulatory plug was observed. The day of mating was designated as day 0 post-coitum.

Group Arrangement:

| Test group | Dose level(mg/kg) | Number assigned |
|---|---|---|
| Control | 0 | 25 (1-25) |
| Low dose | 30 | 25 (26-50) |
| Mid dose | 60 | 25 (51-75) |
| High dose | 120 | 25 (76-100) |

Dosing:

All doses were in a volume of 10 ml/kg of body weight/day prepared daily during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on body weights adjusted daily during the treatment period.

Observations

The animals were checked for mortality or abnormal condition twice daily, minimum. Dams were sacrificed on day 21 of gestation. Examinations at sacrifice consisted of: gross macroscopic examination of all internal organs, with emphasis upon the uterus, uterine contents, position of the fetuses in the uterus and number of corpora lutea. The uteri (and contents) of all females with live fetuses were weighed at necropsy for corrected body weight gain calculations. All uteri of apparently non-pregnant females were placed in aqueous solution on ammonium sulfide to accentuate possible hemorrhagic areas of implantation sites.

The fetuses were examined in the following manner: the fetuses were sexed, weighed individually, examined for gross abnormalities. One half of the fetuses from each litter were examined for visceral and brain abnormalies using Wilson's slicing technique and the rest were cleared in potassium hydroxide and stained with alizarin red S for skeletal examinations.

Statistical Analysis

The following statistical analysis methods were used:

Univariate one-way analysis of variance was used to assess the significance of intergroup differences if the variables could be assumed to follow a normal distribution. The Dunnett many-one-t-test, based on a pooled variance estimate was used for intergroup comparisons (i.e., single treatment groups against the control group).

A one-way univariate analysis of variance based on Wilcoxon ranks together with the Kruskall-Wallis test was applied to the reproduction data parameters.

Fisher's exact test for 2x2 tables was applied if the variables could be dichotomized without loss of information.

Compliance

- A signed Statement of No Confidentiality Claim was provided.

- A signed Statement of Compliance with EPA GLP's was provided.

- A signed Quality Assurance Statement was provided.

C. RESULTS

1. Maternal toxicity

Mortality

No deaths in any dose group was reported.

Clinical observations

No abnormal signs of compound-related toxicity were reported.

Body weight

The investigators supplied the following data:

Body weights were recorded daily from day 0 to 21 p.c. Body weight gains from days 0-6 p.c., 6-11 p.c., 11-16 p.c.,6-16 p.c., 16-21 p.c. and 6-21 p.c. were calculated. Corrected body weight gains were calculated using the formula: body weight on day 21 p.c. - body weight on day 6 p.c. - uterus weight at necropsy on day 21 p.c. = corrected body weight.

Mean body weights were significantly depressed in the HDT as compared to the control group by day 21 (303 gm/HDT vs 320 gm/con.)(see Table Ia). The body weight gains in the HDT dams were somewhat lower during the dosing period or days 6-21 of gestation but there was no indication of a weight rebound in the post-dosing period nor were the corrected body weights significantly different (see Table I).

Table I: Body weight gains and corrected weight (grams/%)[a]

| | Prior to Dosing Period | Dosing Period | Post-dosing period | day6-21 Gestation Period | Corrected[b] BW Gain day6-21(%) |
|---|---|---|---|---|---|
| Group: | | | | | |
| Control | 19(+9.3) | 41(+18.3) | 55(+20.8) | 96(+42.9) | +9.2 |
| LDT | 20(+10.0) | 40(+18.1) | 53(+20.3) | 93(+42.1) | +9.8 |
| MDT | 20(+9.7) | 35(+15.4) | 60(+22.9) | 95(+41.9) | +9.6 |
| HDT | 20(10.0) | 29(+13.1) | 53(+21.2) | 82(+37.1) | +10.0 |

[a] = data extracted from study project number 074057, p.55)
[b] = corrected body weight gain for dosing period = body weight gain for days6-21 minus gravid uterus weight

Mean liver weights and mean liver to body weight ratios were statistically significantly increased in the MDT and HDT dose groups as compared to the controls (see Table Ia) suggesting a possible compound-related toxicological/pharmacological effect.

Table Ia: Organ weights(gm)/organ to body weight ratios(%)

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| Body weights(d. 21) | 320 | 314 | 322 | 303* |
| Liver weights | 11.51 | 11.55 | 12.50* | 12.49* |
| organ:b.wt. | 3.59 | 3.68 | 3.89** | 4.12** |

*/** Dunnett-Test; significant at 0.05 and 0.01 level, resp.

Food consumption

The investigators supplied the following data:

Mean daily food consumption was calculated using the following formula, grams of food consumed per period divided by days per period = mean daily food consumption.

Table II: Food Consumption Data (g/animal/day, %*)[a]

| Group: | Prior to Dosing Period | Day6-15 Period | Post-Dosing Period |
|---|---|---|---|
| Control | 20.6 | 21.4 | 23.0 |
| LDT | 20.1(-2.4) | 20.9(-2.3) | 23.3(+1.3) |
| MDT | 20.5(-0.5) | 19.9(-7.0) | 24.2(+5.2) |
| HDT | 20.8(+1.0) | 18.2(-15.0) | 24.3(+5.7) |

[a] Data extracted from study RCC project number 074057, p. 41
* percent of control values

Mean daily food consumption was decreased but not statistically significant during days 6-15 of the test period with a small increase (not statistically significant) post-dosing.

Gross Pathological Observations

The investigators supplied the following data:

See discussion under observations.

A summary of gross necropsy findings was presented by the investigators (pgs. 102-105). One non-pregnant female of the MDT dose group had dilation of the right renal pelvis with a 2mm urinary bladder stone associated with 2 mm dark red foci in the mucous membrane of urinary bladder. A consistent finding in 9/24 HDT dams was the uterus filled with black/brown colored fluid. This probably is related to the increased resorption of embryos/fetuses (one to several) which was observed in all of these dams.

Cesarean Section Observations:

Table III: Cesarean Section Observations[a]

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #animals assigned | 25 | 25 | 25 | 25 |
| #animals mated/inseminated | 25 | 25 | 25 | 25 |
| Pregnancy rate (%) | 96 | 96 | 88 | 96 |
| Maternal wastage | | | | |
| #died | 0 | 0 | 0 | 0 |
| #died/pregnant | 0 | 0 | 0 | 0 |
| #non pregnant | 1 | 1 | 3 | 1 |
| #aborted | 0 | 0 | 0 | 0 |
| #premature delivery | 0 | 0 | 0 | 0 |
| Total corpora lutea | 357 | 347 | 314 | 370 |
| Corpora lutea/dam | 14.9 | 14.5 | 14.3 | 15.4 |
| Total implantations | 302 | 291 | 277 | 298 |
| Implantations/dam | 12.6 | 12.1 | 12.6 | 12.4 |
| Total live fetuses | 288 | 271 | 256 | 232 |
| Live fetuses/dam | 12.0 | 11.3 | 11.6 | 9.7 |
| Total resorptions | 14 | 20 | 21 | 66 |
| Early | 14 | 20 | 19 | 45 |
| Late | 0 | 0 | 2 | 21 |
| Resorptions/dam | 0.6 | 0.8 | 1.0 | 2.8 |
| Total dead fetuses | 0 | 0 | 0 | 0 |
| Dead fetuses/dam | 0 | 0 | 0 | 0 |
| Mean fetal weight(g) | 4.7 | 4.7 | 4.6 | 4.2 |
| Preimplantation loss(%) | 15.4 | 16.1 | 11.8 | 19.5 |
| Postimplantation loss(%) | 4.6 | 6.9 | 7.6 | 22.1 |
| Sex Ratio (% Male) | 48.3 | 47.2 | 50.8 | 50.4 |

[a] = Data extracted from RCC project 074057, p. 28

Pregnancy rates ranged from 88%(MDT) to 96% (remaining dose groups). No abortions or premature deliveries were noted. Mean corpora lutea counts or mean implantations were not significantly different among the treated groups as compared to the controls. Mean live fetuses/dam were decreased in the HDT group as compared to the controls and lower dose groups. This was due to an increase in both early (embryonic) and late (fetal) embryonic resorptions (i.e., total resorptions: 0.6/dam, control vs 2.8/dam, HDT).

Mean fetal weight was somewhat (not statistically significant) reduced in the HDT as compare with the controls while sex ratios (% males) were not different among the dose groups. The fetal weight depression may be treatment-related since a decrease in mean fetal weight was still observed despite a reduction in litter size in the HDT.

2. Developmental Toxicity

Table IV: External examinations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 288(24) | 271(24) | 256(22) | 232(24) |
| # pups(litters) affected | 0 | 0 | 0 | 2(2) |
| Missing tail | 0 | 0 | 0 | 0.4(4.2)[b] |
| Agnatha(lower jaw), microstomia, anophthalmia | 0 | 0 | 0 | 0.4(4.2) |

[a] = some observations may be group together
[b] = fetal (litter) incidence

External examinations revealed the presence of 2 fetuses in 2 dams with either missing tail or a combination of defects (agnatha, microstomia and anopthalmia). Based upon other developmental effects noted in the HDT, without comparable findings in the controls, these may be compound-related malformations.

Visceral findings (presented below in Table V) indicate findings of excess fluid in the thoracic cavity, primarily in the HDT group (4 fetuses of 2 litters). This may also be considered as a compound-related effect.

Table VI below presents the skeletal findings. There was an increase in the number of fetuses (statistically significant) with nonossified or incompletely ossified bones of the thoracic vertebrae, cervical vertebrae, sacral vertebrae, sternum, forelimbs and hind limbs and an increase in supernumerary ribs. These were primarily observed in the HDT. Skeletal effects observed in both the MDT and HDT were nonossified cervical verterbra 2, vertebral arch 6 (right), digit 1 distal phalanx (left), digit 3 proximal phalanx (left), digit 2 proximal phalanx (right), digit 3 proximal phalanx (right), digit 4 proximal phalanx (right) and toe 5 distal phalanx (right).

Visceral Examinations

Table V: Visceral Examinations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 144(24) | 134(24) | 129(22) | 116(24) |
| Excess fluid in thoracic cavity | 0 | 0.7(4.2)[b] | 0 | 3.4(8.3) |
| Missing tail | 0 | 0 | 0 | 0.9(4.2) |
| Agnatha(lower jaw), microstomia, anophthalmia | 0 | 0 | 0 | 0.9(4.2) |

[a] = some observations may be grouped together
[b] = fetal (litter) incidence

D. DISCUSSION/CONCLUSION

a. Maternal toxicity:

Oral administration of terbuconazole during days 6-15 of gestation in the female Wistar rat produced a small (5%) but statistically significant depression in body weights at the HDT associated with increased liver weights and liver to body weight ratios (both MDT and HDT). The depressed body weights were not clearly associated with an effect, i.e., fetal alterations, upon the dams using corrected body weight gains. Mean food consumption was slightly depressed during compound administration followed by a small post-dosing rebound.

The HDT dams had 9/24 uteri filled with black/brown colored fluid, probably blood and associated with the increased resorptions noted in this dose group.

b. Developmental toxicity:

Terbuconazole produced an increased in postimplantation loss in the form of both embryonic and fetal resorptions in the 120 mg/kg dose group. Statistically significant increases in nonossified or incompletely ossified bones of the thoracic, cervical and sacral verterbrae, sternum, fore- and hind limbs along with increases in supernumberary ribs were observed in the mid and high dose groups. Two separate fetuses of two HDT litters had major malformations of missing tail and agnatha, microstomia and anophthalmia at the HDT.

c.

No significant study deficiencies were noted.

111

Skeletal Examinations

Table VI: Skeletal Examinations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 144(24) | 137(24) | 127(22) | 116(24) |
| THORACIC VERTEBRAE | | | | |
| centrum dumbbell shaped (10-13th) | 2(2)# | 2(2) | 2(2) | 6(4) |
| centrum bipartite (10-12th) | 0 | 0 | 0 | 4(2) |
| CERVICAL VERTEBRAE (Nonossified) | | | | |
| Total litters affected | 18 | 19 | 18 | 23 |
| Number of fetuses(%): | | | | |
| Cervical vertebra 1 | 18(3) | 21(15) | 24(19) | 48(41)** |
| Cervical vertebra 2 | 29(20) | 40(29) | 38(30)* | 48(41)** |
| Cervical vertebra 3 | 9(6) | 10(7) | 12((9) | 16(14)* |
| Cervical vertebra 4 | 0 | 5(4)* | 2(2) | 13(11)** |
| Cervical vertebra 5 | 3(2) | 3(2) | 3(2) | 10(9)* |
| Cervical vertebra 6 | 1(1) | 2(1) | 2(2) | 6(5)* |
| SACRAL VERTEBRAE (Nonossified) | | | | |
| Total litters affected | 18 | 18 | 15 | 21 |
| Number of fetuses(%): | | | | |
| Vertebral arch 6, left | 1(1) | 2(1) | 3(2) | 14(12)** |
| Vertebral arch 6, right | 0 | 2(1) | 6(5)** | 13(11)** |
| Vertebral arch 7, left | 50(35) | 53(39) | 49(39) | 66(57)** |
| Vertebral arch 7, right | 45(31) | 53(39) | 51(40) | 65(56)** |
| STERNUM (Incompletely ossified) | | | | |
| Total litters affected | 18 | 15 | 15 | 19 |
| Number of fetuses(%): | | | | |
| Sternebra 2 | 4(3) | 3(2) | 3(2) | 15(13)** |
| Sternebra 6 | 0 | 0 | 1(1) | 4(3)* |

(continued on next page)

Table VI: Skeletal Examinations (continued from previous page)

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 144(24) | 137(24) | 127(22) | 116(24) |
| SUPERNUMERARY RIBS (One, left or right) Total litters affected | 9 | 11 | 13 | 12 |
| Number of fetuses(%): | | | | |
| Ribs, left | 14(10) | 20(15) | 18(14) | 26(22)** |
| Ribs, right | 15(10) | 23(17) | 19(15) | 24(21)* |
| FORELIMBS, LEFT OR RIGHT (Nonossified) Total litters affected | 23 | 20 | 20 | 19 |
| Number of fetuses(%): | | | | |
| Digit 1 distal phalanx(l) | 27(19) | 36(26) | 37(29)* | 42(36)** |
| Digit 3 proximal phalanx(l) | 0 | 3(2) | 5(4)* | 9(8)** |
| Digit 4 proximal phalanx(l) | 2(1) | 7(5) | 7(6) | 11(9)** |
| Metacarpal 5(l) | 0 | 0 | 2(2) | 4(3)* |
| Digit 5 distal phalanx(l) | 55(38) | 56(41) | 55(43) | 23(20)** |
| Digit 2 proximal phalanx(r) | 27(19) | 33(24) | 39(31)* | 40(34)** |
| Digit 3 proximal phalanx(r) | 0 | 3(2) | 4(3)* | 8(7)** |
| Digit 4 proximal phalanx(r) | 1(1) | 6(4) | 6(5)* | 11(9)** |
| Metacarpal 5(r) | 0 | 0 | 2(2) | 5(4)* |
| Digit 5 distal phalanx(r) | 45(31) | 56(41) | 47(37) | 21(18)* |
| HIND LIMB, LEFT OR RIGHT (Nonossified) Total litters affected | 24 | 24 | 22 | 24 |
| Number of fetuses(%): | | | | |
| Metatarsal 1(l) | 18(13) | 24(18) | 18(14) | 31(27)** |
| Toe 2 proximal phalanx(l) | 107(74) | 92(67) | 96(76) | 103(89)** |
| Toe 3 proximal phalanx(l) | 81(56) | 70(51) | 78(61) | 87(75)** |
| Toe 4 proximal phalanx(l) | 79(55) | 65(47) | 72(57) | 85(73)** |
| Toe 5 distal phalanx(l) | 1(1) | 9(7)** | 5(4) | 7(6)* |
| Metatarsal 1(r) | 18(13) | 24(18) | 20(16) | 32(28)** |
| Toe 2 proximal phalanx(r) | 110(76) | 96(70) | 105(83) | 105(91)** |
| Toe 3 proximal phalanx(r) | 86(60) | 75(55) | 76(60) | 92(79)** |
| Toe 4 proximal phalanx(r) | 81(56) | 71(52) | 74(58) | 91(78)** |
| Toe 5 distal phalanx(r) | 1(1) | 9(7)** | 6(5)* | 7(6)* |

# fetal #(litter #)
*, ** = Fisher's exact test; statistically significant ($p<0.05$ or 0.01)

E. CLASSIFICATION: CORE MINIMUM DATA.

Maternal NOEL = 30 mg/kg/day
Maternal LOEL = 60 mg/kg/day
Developmental Toxicity NOEL = 30 mg/kg/day
Developmental Toxicity LOEL = 60 mg/kg/day

F. RISK ASSESSMENT:

Development of MOS has been determined to be unnecessary at this time.

Appendix 5. Rat Oral Historical Control Data.

Page_____ is not included in this copy.

Pages 118 through 133 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Fetal and litter incidences of skeletal observations in rats [From MRID 419620-02].

| Year of Study | % Fetuses / % litters in study number[a] 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Thoracic vertebra centrum dumbell shaped | | | | | | | | |
| 1988 | 0.6/4.0 | 0.6/4.1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | -[b] |
| 1987[c] | 2.2/12.5 | 0.7/4.0 | 2.2/6.0 | 2.6/16.7 | 0/0 | 0.6/4.0 | 0.8/4.4 | 2.7/12.5 |
| 1986 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1.4/8.3 | 2.3/13.6 | 0/0 |
| 1985 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0.7/4.2 | 0/0 | 0/0 |
| Cervical vertebra No. 2 (Non-ossification) | | | | | | | | |
| 1988 | 14.6/56.0 | 12.8/54.2 | 18.7/58.3 | 16.2/50.0 | 8.7/56.1 | 5.6/52.0 | 8.8/36.0 | - |
| 1987 | 24.5/54.2 | 29.1/80.0 | 22.1/76.0 | 12.8/60.0 | 15.5/64.0 | 13.3/60.0 | 14.7/47.8 | 23.8/58.3 |
| 1986 | 29.6/- | 22.6/- | 34.1/- | 25.0/- | 21.4/64.0 | 20.1/62.5 | 31.5/77.3 | 43.8/73.9 |
| 1985 | 23.6/- | 18.1/- | 35.4/- | 24.1/- | 28.7/- | 30.7/- | 17.3/- | 28.4/- |
| Sacral vertebral arch 6 (R, Non-ossification) ) | | | | | | | | |
| 1988 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| 1987 | 0/0 | 0/0 | 2.2/4 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| 1986 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| 1985 | 0/- | 0/- | 0/- | 0/- | 0/- | 0/- | 0/- | 0/- |
| Digit 4 proximal phalanx (R, Non-ossification) | | | | | | | | |
| 1988 | 2.4/12.0 | 5.4/29.2 | 0.7/4.2 | 2.1/12.5 | 2.9/13 | 6.8/28 | 3.8/16 | - |
| 1987 | 8.6/29.2 | 2.1/12.0 | 4.4/20.0 | 0.6/16.0 | 5.6/20.0 | 3.8/16.0 | 5.4/21.7 | 6.1/29.2 |
| 1986 | 3.5/- | 4.8/- | 9.1/- | 3.8/- | 6.2/12.0 | 0.7/16.7 | 5.4/6.4 | 21.9/47.8 |
| 1985 | 6.0/- | 3.0/- | 8.7/- | 3.1/- | 6.2/- | 8.0/- | 3.9/- | 6.6/- |
| Supernumerary ribs (R): | | | | | | | | |
| 1988 | 8.5/32.0 | 3.4/16.7 | 5.8/20.8 | 24.6/70.8 | 8.7/34.8 | 19.3/64.0 | 8.8/28.0 | - |
| 1987 | 10.8/37.5 | 7.8/28.0 | 12.5/36.0 | 14.7/40.0 | 11.3/44.0 | 14.6/40.0 | 3.9/17.4 | 12.2/54.2 |
| Supernumerary ribs (L): | | | | | | | | |
| 1988 | 7.3/24.0 | 2.7/16.7 | 6.5/20.8 | 21.1/66.7 | 9.4/34.8 | 16.1/56.0 | 8.2/20.0 | - |
| 1987 | 12.9/41.7 | 8.5/32.0 | 13.2/32.0 | 12.8/32.0 | 10.6/44.0 | 12.7/32.0 | 3.1/17.4 | 9.5/50.0 |

[a] The historical data covers: 1988: 7 studies, 1052 skeletons, & 170 litters; 1987: 8 studies, 1148 skeletons, & 195 litters; 1986: 8 studies, 1108 skeletons, & 189 litters; 1985: 8 studies, 1323 skeletons, & 763 litters; for a total of 31 studies, 4631 skeletons and 763 litters [From MRID 419620-02]

[b] No data.

[c] The data for 1987 covers thoracic/lumbar vertebral centrum(a) dumbell shaped/bipartite/abnormally ossified, thus it represents an upper limit for thoracic dumbell shaped incidence and is not truly comparable with the data for the other three years.

134

Appendix 6. Rat Dermal Developmental Toxicity Study.

Appendix 6. Rat Dermal Developmental Toxicity Study.

Primary Review by: James N. Rowe, Ph.D. James N. Rowe 9/27/90
Review Section I, Toxicology Branch II/HED
Secondary Review by: Yiannakis M. Ioannou, Ph. D. 9/27/90
Section Head, Review Section I, Toxicology Branch II/HED

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat
Guideline: 83-3

EPA Identification No.s: EPA MRID No. 414508-01
EPA ID No. 3125-GIG
EPA Record No. 263,443
EPA Pesticide Chemical Code
Caswell No. 463P
HED Project No. 0-1188
Document No. 98359

Test Material: HWG 1608

Synonyms: Tebuconazole (proposed name)

Sponsor: Mobay Corporation

Study Number(s): 17089

Testing Facility: BAYER AG
Institute of Toxicology
Friedrich-Ebert-Strasse 217-333
Federal Republic of Germany

Title of Report: Study for Embryotoxic Effects on Rats after Dermal Administration

Author(s): Dr. M. Renhof

Report Issued: August 30, 1988

Bibliographic Citation: (for standards)

Conclusions:

Technical Tebuconazole was topically applied to groups of approximately 25 pregnant rats during gestation days 6-15 at nominal dose levels of 0, 100, 300 and 1000 mg/kg/day to a 25 $cm^2$ area. No evidence of maternal toxicity (changes in body weights, corrected body weights, food consumption, clinical signs, pathology, deaths, abortions, premature deliveries) were noted at any dose level. No developmental toxicity was noted at any dose level based upon indices of mean corpora lutea/dam, implantations/dam, live or dead fetuses/dam, resorptions/dam (early, late), mean fetal weights, sex ratios (% male), mean

crown-rump length (cm), mean runts/dam, variations or malformations. The adequacy of this study remains to be determined since it is unclear whether the dermal exposure regimen resulted in sufficient exposure to the test compound.

Core Classification: Supplementary. Additional information on the dermal absorption and pharmacokinetics of Tebuconazole in the pregnant rat are required to determine if dosing during the period of major organogenesis (days 6-15 of gestation) is appropriate.

A. Materials

A copy of the "materials and methods" section from the investigators report is appended.

Test Compound: Purity: 97.4%
Description: Solid, grey-white, powdery crystals
Lot No.: 16012/86
Contaminant: not listed

Vehicle(s): 1% aqueous Cremophor EL emulsion

Test Animal(s): Species: rat
Strain: Bor: WISW (SPF Cpb)
Source: Winkelmann, Borchen
Age: sexually mature
Weight: ≥300 g(males); 194-242 g(females)

B. Study Design

This study was designed to assess the developmental toxicity potential of HWG 1608 when administered dermally to pregnant rats on gestation days 6 through 15, inclusive.

Mating

Mating took place overnight, one male being placed with two females in a Makrolon cage type III. If sperm were found in the vaginal smear on the morning after mating, this day was considered day zero of gestation.

Group Arrangement:

Animals were randomized with computerized random numbers.

| Test Group | Dose Level (mg/kg) | Number Assigned |
|---|---|---|
| Control | 0 | 25 |
| Low Dose | 100 | 25 |
| Mid Dose | 300 | 25 |
| High Dose | 1000 | 25 |

Dosing:

All doses were given a volume of 2 ml/kg of body weight/day prepared in a 1% aqueous Cremophor EL emulsion during the dosing period. The material was applied to a gauze dressing which was then placed on an area of shaved skin (approx. 5 cm x 5 cm) for six hours and then removed and washed with lukewarm water. The dosing solutions were analyzed for concentration and stability. Tebuconazole was stable when stored up to 7 days (refrigerated at 4°C). Samples of nominal administered doses of 50, 150 and 500

mg/ml were analyzed on 3/20, 4/21 and 5/15/87 and ranged from 87 to 107% of nominal. Dosing was based on current gestation day body weight.

Observations

The animals were checked for mortality or abnormal condition daily and the treated skin was assessed daily for irritation after each application. Dams were sacrificed on day 20 of gestation. Examinations at sacrifice consisted of:

1) autopsy of dams,
2) determination of implantation count,
3) determination of corpora lutea count,
4) determination of uterus weight,
5) determination of number of live and dead fetuses or embryos (dams without live fetuses were assessed as non-pregnant),
6) determination of all the live fetuses' sex,
7) determination of individual fetus weight for all live fetuses and runts,
8) determination of individual placenta weight,
9) determination of fetuses' crown/rump length,
10) detailed examination of all fetuses for external malformations,
11) examination of a number of fetuses for visceral malformations,
12) appraisal of abdominal and thoracic organs, followed by clearing of fetuses and skeletal examination.

The fetuses were examined in the following manner. For visceral malformations, the modified method of Wilson was used for approximately 50% of the fetuses. Exenteration of the remaining fetuses was followed by clearing with diluted potassium hydroxide solution, staining of the bone system with alizarin red S and appraisal of the bone system by the method of Dawson.

Historical control data were provided to allow comparison with concurrent controls but appeared to present only fetal incidence and not litter incidence. (see attached data).

Statistical analysis

The following statistical analysis methods were employed.

1) Wilcoxon's non-parametric rank sum test, e.g., weight gains, number of implantations, fetuses and resorptions,
2) Chi Square test (Yate's method modified), e.g., number of runts,
3) Chi Square test (Yates' or Fisher's "exact test", depending on incidence expected) for rates of fertilized and pregnant animals.

Significance set at $p<0.05$ level.

Compliance

A signed Statement of Confidentiality Claim was provided.

A signed Statement of compliance with EPA GLP's was provided.

A signed Quality Assurance Statement was provided.

Results

Maternal Toxicity

Mortality

No animals died during the study period.

Clinical Observations

Wounds were observed in many of the animals of all dose groups, apparently due to the dressing rubbing the skin.

The majority of animals in all dose groups did not have skin irritation from compound application. Four, 4, 4 and 7 rabbits in the respective dose groups did have some dermal reactions. In the controls, very slight to well-defined (1 dam) erythema was observed on one or 2 days of topical application. The LDT group had very slight erythema observed on 1 day of the dosing period while the MDT dose group had 3 dams with very slight erythema on 1-3 days of the exposure period. One MDT dam had very slight to moderate/severe erythema on 5 days of exposure associated with very slight edema (1 day only). The HDT group had 5 animals with slight redness on 1-3 days of exposure and 1 animal experienced very slight to well-defined erythema associated with very slight edema on 7-8 days of dermal application. All skin reactions were noted only during compound administration. These reactions are not expected to significantly affect the dermal barrier or adversely affect the outcome of this study.

Body Weight

The investigators supplied the following data:

Table I: Body Weight Gains (grams)[a]

| Group: | Prior to Dosing Period | Dosing Period | Post Dosing Period | Entire Gestation Period |
|---|---|---|---|---|
| Control | -- | 14.3 | -- | 75.0 |
| LDT | -- | 13.8 | -- | 78.1 |
| MDT | -- | 16.5 | -- | 80.4 |
| HDT | -- | 16.2 | -- | 77.5 |

a = Data extracted from study number T6025171, pages 45-48

Table IA: Mean Body Weights(g±SD)

| | day 0 | day 6 | day 15 | day 20 |
|---|---|---|---|---|
| Control | 213.6(10.7) | 234.1(11.9) | 248.4(14.0) | 288.6(18.7) |
| LDT | 213.8(8.6) | 234.7(8.7) | 248.5(11.2) | 291.9(19.0) |
| MDT | 216.7(9.7) | 234.0(9.3) | 250.5(12.2) | 297.1(16.3) |
| HDT | 217.4(10.9) | 235.8(11.8) | 252.0(13.5) | 294.9(19.1) |

Mean body weights were not significantly different prior to dermal application of Tebuconazole (day 0) or at any time period during (days 6, 15) or after exposure (day 20). There was no statistically significant difference in mean weight gains observed in any treatment group during either the dosing period or the entire gestation period. Mean uterine weights (not presented in tables) were similar among the treatment groups, i.e., 52.2 g, 53.9 g, 59.7 g and 54.1 g, respectively.

Food Consumption

The investigators supplied the following data:

Table II: Food Consumption Data (g/animal)[a]

| Group: | Prior to Dosing Period (0-6) | Dosing Period (6-11) | Dosing Period (11-16) | Post-Dosing Period (16-20) | Entire Gestation Period (0-20) |
|---|---|---|---|---|---|
| Control | 110 | 84 | 101 | 89 | 385 |
| LDT | 112 | 86 | 101 | 91 | 389 |
| MDT | 109 | 86 | 100 | 89 | 384 |
| HDT | 108 | 84 | 103 | 88 | 383 |

[a] = Data extracted from study T6025171, pages 49-52

There were no significant differences related to Tebuconazole application for mean food consumption values (g/animal) prior to dosing, during the dosing period , post-dosing or when considered for the entire gestation period. This is consistent with the absence of body weight alterations due to compound treatment.

Gross Pathological Observations

The investigators reported no compound-related necropsy findings. Intestinal worms were reported in several animals in all treatment groups.

Cesarean section Observations

Table III: Cesarean Section observations[a]

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #Animals Assigned | 25 | 25 | 25 | 25 |
| #Animals Mated/Insmntd | 25 | 25 | 25 | 25 |
| Pregnancy Rate (%) | 96 | 92 | 88 | 92 |
| Maternal Wastage | | | | |
| #Died | 0 | 0 | 0 | 0 |
| #Died/pregnant | 0 | 0 | 0 | 0 |
| #Non pregnant | 1 | 2 | 3 | 2 |
| #Aborted | 0 | 0 | 0 | 0 |
| #Premature Delivery | 0 | 0 | 0 | 0 |
| Total Corpora Lutea | 310 | 294 | 286 | 292 |
| Corpora Lutea/dam | 12.9(1.5) | 12.8(1.4) | 13.0(1.1) | 12.7(1.0) |
| Total Implantation | 259 | 253 | 262 | 255 |
| Implantations/Dam | 10.8(3.0) | 11.0(2.4) | 11.9(1.7) | 11.1(1.8) |
| Total Live Fetuses | 230 | 226 | 242 | 225 |
| Live Fetuses/Dam | 9.6 | 9.8 | 11.0 | 9.8 |
| Total Resorptions | | | | |
| Early | 1 | 1 | 2 | 4 |
| Late | 27 | 25 | 17 | 26 |
| Resorptions/Dam | 1.2 | 1.1 | 0.9 | 1.3 |
| Total Dead Fetuses | 0 | 0 | 0 | 0 |
| Dead Fetuses/Dam | 0 | 0 | 0 | 0 |
| Mean Fetal Weight (gm) | 3.42 | 3.43 | 3.39 | 3.46 |
| Preimplantation Loss(%) | 16.5 | 14.0 | 8.3 | 12.7 |
| Postimplantation Loss(%) | 11.2 | 10.7 | 7.6 | 11.8 |
| Sex Ratio (% Male) | 53 | 46 | 54 | 54 |
| Crown-rump length(cm) | 3.47 | 3.48 | 3.45 | 3.51 |
| Runts/dam[b] | 0.38 | 0.26 | 0.41 | 0.13 |

[a] = Data extracted from study T6025171, pages 15, 53-144, Table 1, pages 154-158)

b = Runts have a weight less than 2.64 g (arithmetic mean - 2 SD of control)

No compound or dose-related effects were observed for

indices of maternal wastage (deaths, abortions, non-pregnancies or premature deliveries), mean corpora lutea/dam, implantations/dam, live or dead fetuses/dam, resorptions/dam (early, late), mean fetal weights, sex ratios (% male), mean crown-rump length (cm) or mean runts/dam.

2. Developmental Toxicity

**Table IV: External/visceral/skeletal malformations***

| Observations | Control | Low Dose | Mid Dose | High Dose |
|---|---|---|---|---|
| #pups(litters) examined | 230(24) | 226(23) | 242(22) | 225(23) |
| #pups(litters) affected | 4(4) | 1(1) | 3(2) | 2(2) |
| Abdomen -closed fissure | 1(1)[a] | 0(0) | 0(0) | 0(0) |
| Cleft Palate | 1(1) | 0(0) | 0(0) | 0(0) |
| Eye -microphthalmia (left, right) | 2(2) | 0(0) | 2(2) | 0(0) |
| Kidney -hydronephrosis (left, right) | 1(1) | 1(1) | 0(0) | 0(0) |
| Scapula, long bones -dysplasia | 1(1) | 0(0) | 1(1) | 0(0) |
| Testes -cryptorchism | 0(0) | 0(0) | 0(0) | 1(1) |
| Vertebral column/ribs -asymmetric verterbrae, fused ribs | 0(0) | 0(0) | 0(0) | 1(1) |

([a]) fetal [litter] incidence
* taken from page 16 of study report T6025171

Various external, visceral or skeletal malformations (see table above) were noted among the different dose groups including cleft palate, microphthalmia, hydronephrosis, dysplasia, asymmetric vertebra/fused ribs, cryptorchism (testes) and dysplasia of the scapula, long bones. None of these findings were biologically or statistically significant changes related to compound administration. Most of these findings were reported as occurring in the historical control data for 1986 and 1987.

Table IV: Skeletal Examinations*

| Observations* | Control | Low Dose | Mid Dose | High Dose |
|---|---|---|---|---|
| #pups(litters) examined | 122(24) | 119(23) | 127(22) | 120(23) |
| #pups(litters) affected | 71(22) | 54(22) | 71(22) | 62(22) |
| Sternum | | | | |
| -bone centers absent | 12(8)[a] | 7(7) | 13(9) | 4(3) |
| -slight fissure | 0(0) | 0(0) | 1(1) | 0(0) |
| Vertebra column | | | | |
| -vertebrae | 46(19) | 36(18) | 50(22) | 43(20) |
| Ribs | | | | |
| -13th rib | 1(1) | 0(0) | 0(0) | 1(1) |
| -uneven | 10(8) | 12(10) | 8(7) | 7(5) |
| Pelvis | | | | |
| -bone centers absent | 1(1) | 1(1) | 1(1) | 0(0) |
| Metatarsals/metacarpals | | | | |
| -less than 3 each | 0(0) | 1(1) | 1(1) | 0(0) |
| Skull | | | | |
| -rudimentary bone ctrs | 24(13) | 20(12) | 23(14) | 17(10) |
| Fontanelle | | | | |
| -extended | 2(2) | 0(0) | 2(2) | 3(2) |
| Hyoid bone | | | | |
| -absent, split bone ctrs. | 15(9) | 5(5) | 12(10) | 7(5) |

* taken from summary and individual data tables on pages 162-257.
([a]) fetal [litter] incidence

Tebuconazole did not increase the fetal or litter incidence of various growth-related findings in the sternum, vertebra, ribs, pelvis, metatarsals/-carpals, skull, fontanelle or hyoid bone.

D. Discussion/Conclusions

a. Maternal Toxicity:

Dermal application of Tebuconazole at doses up to 1 gm/kg/day (limit dose for oral developmental toxicity studies) did not produce any evidence of maternal toxicity.

b. Developmental Toxicity:

i. Deaths/Resorptions:

No apparent compound or dose-related effects were noted.

ii. Altered Growth:

No apparent compound or dose-related effects were noted.

iii. Developmental Anomalies:

No apparent compound or dose-related effects were noted.

iv. Malformations:

No apparent compound or dose-related effects were noted.

D. Study Deficiencies:

1) Uncertainty regarding the validity of the duration of dermal dosing

Although presently there are no testing guidelines for dermal teratology studies, recommendations have been recently made by EPA and other scientists that 1) dermal developmental toxicity studies without any indication of maternal or developmental toxicity are inadequate for risk assessment unless accompanied by absorption data, 2) absorption data and limited pharmacokinetic data should be collected in every dermal developmental toxicity study, and 3) dermal developmental toxicity studies in which skin irritation is too marked should be considered inadequate for risk assessment (Kimmel, C., Francis, E. Proceedings of the Workshop on the Acceptability and Interpretation of Dermal Developmental Toxicity Studies, Fund. Appl. Tox., 14:386-398, 1990).

This study does not generally indicate that marked skin irritation (moderate erythema and/or marked moderate edema) occurred. However, it is unclear whether, 1) any actual compound was absorbed (in the pregnant rat) and whether, 2) the dosage regimen was such to maximize the potential for dermal absorption to occur. As noted in the reference above, "When skin penetration is relatively rapid and complete, the standard treatment period which covers major organogenesis is probably

adequate. If skin penetration is very poor, either a prolonged treatment period beginning before or immediately after mating or use of another route of administration which results in greater systemic exposure may be warranted."

A dermal absorption study has recently been submitted for male rats by the registrant (MRID No. 409959-13) and indicates that when 10 mg/rat (547 $\mu g/cm^2$) is applied for 4 to 8 hours to the skin, approximately 65% of the material remains bound and 1.3 to 1.4 % is absorbed. Smaller exposure doses (0.604 to 52.4 $ug/cm^2$) resulted in lower skin residues (30-50%) and higher systemic doses (8 to 22%). Since the skin residue is potentially absorbable, considerable variation may occur in the systemic concentrations achievable at different topical application doses. Furthermore, the time period of topical application could make a significant difference in the actual absorbed dose due to the kinetics of uptake into the blood from the reservoir of test material located in the skin. Thus, it may be most appropriate to dose pregnant animals from the day after confirmation of mating until sacrifice in order to maximize the potential for fetal exposure to Tebuconazole instead of during the period of major organogenesis.

2) Confirmation of reported malformations

No individual animal data were provided to allow confirmation of the malformations presented in the report.

3) Apparent lack of litter incidence data for historical control data submitted

E. Core Classification: Core Supplementary Data.

Maternal NOEL = To be determined
Maternal LOEL = To be determined
Developmental Toxicity NOEL = To be determined
Developmental Toxicity LOEL = To be determined

F. Risk Assessment: Not applicable at this time. Based upon the low NOEL observed in rats, rabbits and mice oral studies, it may be appropriate to perform an estimate of Margins of Exposure once the validity of the study is determined.

**Appendix 7.** Rabbit Range-Finding Developmental Toxicity Study.

Appendix 7. Rabbit Range-Finding Developmental Toxicity Study.

Reviewed by: James N. Rowe, Ph.D., James N. Rowe 12/21/88
Review Section I
Tox. Branch: Herb. Fung. Antimicrobial Support (TS-769C)
Secondary reviewer: Quang Q. Bui, Ph.D.
Review Section I, Tox. Branch: H.F.A.S. (TS-769C) Quang Bui 12/22/88

DATA EVALUATION REPORT

STUDY TYPE: Dose-ranging rabbit teratology (83-3) TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 407009-44

TEST MATERIAL: HWG 1608 TECHNICAL; Batch No. 16002/85; colorless crystals; purity of 98.2%; stored at room temperature in dark

SYNONYMS: FOLICUR@;(terbuconazole)

STUDY NUMBER(S): report no. R4321; Lab. proj. ID no. 97400; RCC proj. no. 074068

SPONSOR: BAYER AG, Institut fuer Toxikologie Landwirtschaft, Fachbereich Toxikologie, D 5600 Wuppertal 1, FRG

TESTING FACILITY: RCC, Research & Consulting Company AG and RCC, Umweltchemie AG, CH 4452 Itingen/Switzerland

TITLE OF REPORT: Dose range-finding embryotoxicity study (including teratogenicity) study with HWG 1608 TECHNICAl in the rabbit.

AUTHOR(S): H. Becker (study director)

REPORT ISSUED: February 4, 1987

CONCLUSIONS:

Oral gavage of Chinchilla rabbits during days 6-18 of presumed gestation at 0, 30, 100 and 300 mg/kg/day produced reduced body weight gains and food consumption during the dosing period in the high and/or mid dose groups. In the high dose group the single pregnant doe had 100% implantations losses while the mid dose animals had an increase in preimplantation losses and post-implantation losses (due to increased fetal resorptions). Based upon these findings, the dosages set in the full developmental toxicity test were 10, 30 and 100 mg/kg/day.

These data are designated as Core supplementary since it is only intended as a range-finding study.

MATERIALS AND METHODS:

Chinchilla rabbits(Kfm: CHIN, hybrids, SPF quality) were acclimatized for 7 days under test conditions after a veterinary examinination and were 18 weeks of age at delivery. Body weights upon receipt were 3000 gms(+/-500 gms). Twelve mated females, 3 per group were used. Animals were housed individually in stainless steel cages with automatic cleaning system and fed pelleted Kliba 341 rabbit maintenance diet. Water was available ad libitum.

After acclimation, the females were paired overnight with sexually mature males (1:1). After mating was observed (method of determination not stated), the female was removed and housed individually with the day designated as day 0 post coitum. Animals were assigned to the different groups by a random algorithm. Test and control females were gavaged daily (4 ml/kg) from day 6-18 post-coitum in the morning with the following dosage regimen: Group 1/0, Group 2/30, Group 3/100 and Group 4/ 300 mg/kg. Test mixtures were prepared daily.

Mortality (twice daily, minimum), clinical signs(twice daily, minimum), body weights(daily), food consumption(6,11, 15, 19, 24, 28 p.c.), postmortem examinations of dams (day 28 sacrifice), with emphasis upon the uterus, uterine contents, position of the fetuses in the uterus and number of corpora lutea and fetal examination for sexes, weights and gross external abnormalities were determined. Internal examinations of thorax, abdomen, pelvis, organs and cranii of all fetuses were performed. Uteri and contents of all pregnant females were weighed on the scheduled day of necropsy and used to determine the corrected body weight gain. If no implantation sites were evident, the uteri were placed in ammonium sulfide to accentuate possible hemorrhagic sites.

Food consumption data, body weight data and caesarean section data were recorded on-line and evaluated by computer programs. The additional data were recorded on data sheets. Body weight gain from days 0-6 p.c., 6-11 p.c., 11-15 p.c., 6-19 p.c., 19-24 p.c., 24-28 p.c. and 6-28 p.c. were calculated. Corrected body weight gain was calculated as follows: (weight on day 28 p.c.)- (weight on day 6 p.c.) - (uterus wt.). Mean food consumption/ day was calculated as the average (g) per period fed (days). Mean and standard deviations were applied when found appropriate.

RESULTS/CONCLUSIONS:

MORTALITY/CLINICAL SIGNS/NECROPSY

No deaths or adverse signs of toxicity were reported. No gross pathology were noted in any group at necropsy on day 28 p.c.

MATERNAL BODY WEIGHTS

Mean body weight gain was depressed in the HDT as compared to the control for the treatment period of 6-19 days (+210 gm/control vs -157 gm/HDT). This was followed by a rebound in mean body weight gain for days 19-24 and 24-28 as compared to controls (e.g., days 24-28: +30 gms/control vs +104 gms/HDT). Corrected body weight gains could not be determined in the HDT since only 1/3 does was pregnant and this animal had only implantation site scars at necropsy.

MATERNAL FOOD CONSUMPTION

Mean food consumption (g/animal/day) was reduced in the mid and high dose animals as compared to controls during compound administration on days 6-19 by 14 and 50%, respectively. This was followed by rebounds in these dose groups in food consumption for days 19-24 and 24-28 (e.g., days 24-28: +80 and +82%, respectively).

REPRODUCTIVE/FETAL DATA

As mentioned above, only 1/3 does was pregnant in the high dose group and no live fetuses were observed in this animal. There was an apparent increase in mean per dam preimplantation loss in the MDT as compared to the controls (0.3, control vs 1.7/MDT). Per dam live fetuses (no dead fetuses were seen in any group) were lower in the MDT than the controls (1.0, control vs 2.5, MDT). This was due to an elevation in fetal resorptions (0/dam, control vs 1.0/dam, MDT). Mean fetal weights were not different among the available dose groups nor were fetal sex ratios.

**Appendix 8.** Rabbit Oral Developmental Toxicity Study.

Appendix 8. Rabbit Oral Developmental Toxicity Study.

**Reviewed by:** James N. Rowe, Ph.D. James N. Rowe 12/22/88
**Review Section:** I
**Tox. Branch:** Herb. Fung. Antimicrobial Support (TS-769C)
**Secondary reviewer:** Quang Q. Bui, Ph.D. Quang Q Bui 12/23/88
**Review Section I, Tox. Branch:** H.F.A.S. (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Rabbit teratology (83-3) TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 407009-45

TEST MATERIAL: HWG 1608 TECHNICAL; Batch No. 16002/85; colorless crystals; purity of 98.2%; stored at room temperature in dark

SYNONYMS: FOLICUR@;(terbuconazole)

STUDY NUMBER(S): RCC proj. no. 074070; BAYER T 0023302; 96764

SPONSOR: BAYER AG, Institut fuer Toxikologie Landwirtschaft, Fachbereich Toxikologie, D 5600 Wuppertal 1, FRG

TESTING FACILITY: RCC, Research & Consulting Company AG and RCC, Umweltchemie AG, CH 4452 Itingen/Switzerland

TITLE OF REPORT: Embryotoxicity (including teratogenicity) study with HWG 1608 TECHNICAl in the rabbit.

AUTHOR(S): H. Becker (study director)

REPORT ISSUED: February 26, 1987

CONCLUSIONS:

Oral administration of terbuconazole at 0, 10, 30 and 100 mg/kg/day during days 6-18 of gestation in the Chinchilla rabbit produced a minimal depression in mean body weight gain at the HDT associated with a decrease in food consumption. Thus, it is not apparent that any maternal toxicity was exhibited. There was an increase in postimplantation losses (both early and late resorptions), small decreases in the rate of ossification in the right and left digits or toes of the fore- and hindlimb, and frank malformations in 8 fetuses of 5 litters (peromelia, and palatoschisis, malrotation of right hindlimb, agenesis of claws) in the HDT as compared to concurrent controls or historical data. These effects are considered compound-related. Maternal toxicity NOEL is set at 30 mg/kg/day. The developmental toxicity NOEL is set at 30 mg/kg/day, the LOEL at 100 mg/kg/day.

CORE: MINIMUM. It is requested that the investigators explain the meaning of the skeletal finding stated as "various bones".

A. MATERIALS

(A photocopy of the materials and methods section is appended).

Test compound: Purity: 98.3%
Description: colorless crystals
Lot No: 16002/85
Contaminants (list in CBI appendix): N/A

Vehicle(s): Distilled water with 0.5% Cremophor EL (BASF)

Test animals: Species: rabbit
Strain: Chinchilla rabbit (Kfm: CHIN, hybrids, SPF Quality)
Source: KFM, Kleintierfarm Madoerin AG, CH 4414 Fuellinsdorf/Switzerland
Age: 13 to 18 weeks (at pairing)
Weight: 2426-4231 (post-coitum)

B. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of terbuconazole, when administered by gavage from gestational days 6 through 18, inclusive.

Mating:

After acclimatization for 7 days, females were housed with males (1:1) overnight until mating was observed. After mating, the females were removed and caged individually. The day of mating was designated as day 0 post-coitum.

Group Arrangement:

| Test group | Dose level(mg/kg) | Number assigned |
|---|---|---|
| Control | 0 | 16 (1-16) |
| Low dose | 10 | 16 (17-32) |
| Mid dose | 30 | 16 (33-48) |
| High dose | 100 | 16 (49-64) |

Dosing:

All doses were in a volume of 4 ml/kg of body weight/day prepared daily during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on body weights adjusted daily during the treatment period.

Observations

The animals were checked for mortality or abnormal condition twice daily, minimum. Dams were sacrificed on day 28 of gestation. Examinations at sacrifice consisted of: gross macroscopic examination of all internal organs, with emphasis upon the uterus, uterine contents, position of the fetuses in the uterus and number of corpora lutea. The uteri (and contents) of all pregnant females were weighed at necropsy for corrected body weight gain calculations. All uteri of apparently non-pregnant females were placed in aqueous solution on ammonium sulfide to accentuate possible hemorrhagic areas of implantation sites. Liver weights were recorded.

The fetuses were examined in the following manner: the fetuses were sexed, weighed individually, examined for gross abnormalities and prepared for internal examination. Fetal body cavities (thorax, abdomen, pelvis) and the organs were examined; fetuses were sexed. Crania of all fetuses were examined for ossification. Heads were fixed in trichloroacetic acid and formaldehyde and serially sectioned and examined. Trunks were cleared in potassium hydroxide and stained with alizarin red S for skeletal examinations.

Statistical Analysis

The following statistical analysis methods were used:

Univariate one-way analysis of variance was used to assess the significance of intergroup differences if the variables could be assumed to follow a normal distribution. The Dunnett many-one t-test, based on a pooled variance estimate was used for intergroup comparisons (i.e., single treatment groups against the control group).

A one-way univariate analysis of variance based on Wilcoxon ranks together with the Kruskall-Wallis test was applied to the reproduction data parameters.

Fisher's exact test for 2x2 tables was applied if the variables could be dichotomized without loss of information.

Compliance

- A signed Statement of No Confidentiality Claim was provided.

- A signed Statement of Compliance with EPA GLP's was provided.

- A signed Quality Assurance Statement was provided.

C. RESULTS

1. Maternal toxicity

Mortality

No deaths attributable to treatment in any dose group was reported. One female death in the HDT was reported due to intubation error (p. 21 of report).

Clinical observations

No abnormal signs of compound-related toxicity were reported.

Body weight

The investigators supplied the following data:

Body weights were recorded daily from day 0 to 28 p.c. Body weight gains from days 0-6 p.c., 6-11 p.c., 11-15 p.c.,6-19 p.c., 19-24 p.c. and 6-28 p.c. were calculated. Corrected body weight gains were calculated using the formula: body weight on day 28 p.c. - body weight on day 6 p.c. - uterus weight at necropsy on day 28 p.c. = corrected body weight.

Mean body weight gains are presented below.

Table I: Body weight gains and corrected weight (grams/%)[a]

| | Prior to Dosing (d0-6) | Dosing Period (d6-18) | Post-dosing day19-24 | day6-28 Gestation period | Corrected[b] BW Gain day6-28(%) |
|---|---|---|---|---|---|
| Group: | | | | | |
| Control | 205(+7.3) | 319(+10.6) | 104(+3.1) | 464(+15.4) | 1.4 |
| LDT | 235(+8.5) | 262(+8.8) | 98(+3.0) | 442(+14.8) | 0.5 |
| MDT | 242(+8.3) | 302(+9.6) | 95(+2.8) | 453(+14.4) | 0.6 |
| HDT | 205(+6.7) | 198(+6.1) | 74(+2.1) | 341(+10.5) | -0.3 |

[a] = data extracted from study project number 074070, p.55); % = percent of weight at beginning of stated period
[b] = corrected body weight gain for dosing period = body weight gain for days 6-28 minus gravid uterus weight; % of day 6 weight

Mean body weights gains were depressed somewhat in the HDT as compared to the controls during the dosing period but there was no evidence of a rebound in body weights following treatment. HDT corrected body weight gain (%) was slightly lower than the controls.

Mean organ weights(gms) and organ to body weight ratios (%) are given below in Table Ia. Neither parameter was affected in any treatment group as compared to the controls.

Table Ia: Organ weights(gm)/organ to body weight ratios(%)

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| Body weights(d. 28) | 3470 | 3464 | 3571 | 3598 |
| Liver weights | 81.88 | 74.44 | 76.61 | 84.62 |
| organ:b.wt.(%) | 2.36 | 2.15 | 2.14 | 2.35 |

Food consumption

The investigators supplied the following data:

Mean daily food consumption was calculated using the following formula, grams of food consumed per period divided by days per period = mean daily food consumption.

Table II: Food Consumption Data (g/animal/day, %*)[a]

| | Prior to Dosing Period | Day6-18 Period | Post-Dosing Period day 19-24 | day 24-28 |
|---|---|---|---|---|
| Group: | | | | |
| Control | 195 | 207 | 191 | 119 |
| LDT | 199(+2.1) | 199(-3.9) | 157(-17.8) | 118(-0.8) |
| MDT | 201(+3.1) | 203(-1.9) | 186(-2.6) | 142(+19.3) |
| HDT | 202(+3.6) | 182(-12.1) | 197(+3.1) | 158(+32.8) |

[a] Data extracted from study RCC project number 074070, p. 59
* percent of control values

Food consumption was depressed in the HDT during the dosing period, days 6-18, (-12.1 % of controls) with an apparent rebound during days 24-28 in both the mid and high dose groups.

Gross Pathological Observations

The investigators supplied the following data:

See discussion under observations.

A summary of gross necropsy findings was presented by the investigators (pgs. 95-98).

No compound-related effects were noted. One doe in the LDT had pus in the right uterine horn (#29). In the HDT one female had slight indentations on the kidney surface (both) (#57) and one doe had several dark-red foci (ca. 5 mm diameter) in the lungs (# 61).

**Cesarean Section Observations:**

**Table III: Cesarean Section Observations[a]**

| Dose: | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| #animals assigned | 16 | 16 | 16 | 16 |
| #animals mated/inseminated | 16 | 16 | 16 | 16 |
| Pregnancy rate (%) | 94 | 88 | 94 | 88 |
| Maternal wastage | | | | |
| #died | 0 | 0 | 0 | 0 |
| #died/pregnant | 0 | 0 | 0 | 1* |
| #non pregnant | 1 | 2 | 1 | 2 |
| #aborted | 0 | 0 | 0 | 0 |
| #premature delivery | 0 | 0 | 0 | 0 |
| Total corpora lutea | 128 | 125 | 140 | 132 |
| Corpora lutea/dam | 8.5 | 8.9 | 9.3 | 9.4 |
| Total implantations | 121 | 116 | 133 | 124 |
| Implantations/dam | 8.1 | 8.3 | 8.9 | 8.9 |
| Total live fetuses | 111 | 113 | 122 | 90 |
| Live fetuses/dam | 7.4 | 8.1 | 8.1 | 6.4 |
| Total resorptions | 10 | 3 | 11 | 34 |
| Early | 2 | 2 | 5 | 12 |
| Late | 8 | 1 | 6 | 22 |
| Resorptions/dam | 0.7 | 0.2 | 0.7 | 2.4 |
| Total dead fetuses | 0 | 0 | 0 | 0 |
| Dead fetuses/dam | 0 | 0 | 0 | 0 |
| Mean fetal weight(g) | 35.1 | 33.5 | 35.0 | 33.0 |
| Preimplantation loss(%) | 5.5 | 7.2 | 5.0 | 6.1 |
| Postimplantation loss(%) | 8.3 | 2.6 | 8.3 | 27.4 |
| Sex Ratio (% Male) | 53.2 | 50.4 | 50.8 | 51.1 |

[a] = Data extracted from RCC project 074070, p. 29-31
* intubation error

Pregnancy rates ranged from 88 % to 94 % and were considered acceptable. Mean number of corporea lutea/dam and implantations/dam were not different among the dose groups. There was a reduction in live fetuses/dam observed in the high dose group as compared to the controls (7.4, control vs 6.4, HDT) which was due to an increase in total resorptions/dam (early, late) (0.7, control vs 2.4, HDT). Preimplantation losses, mean fetal weights and sex ratios were not different among the dose groups.

2. Developmental Toxicity

Table IV: External and/or head examinations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 111(15) | 113(14) | 122(15) | 90(14) |
| # pups(litters) affected | 0 | 0 | 0 | 8(5)[b] |
| Peromelia: 1) rt. foreleg, no forepaw, 2) rt. foreleg, foreleg shortened with only stump of forepaw, 3) left foreleg, small stump present | 0 | 0 | 0 | 5(4) |
| Palatoschisis | 0 | 0 | 0 | 1(1) |
| Malrotation of rt. hindlimb;hydrocephalus internus (both hemispheres) with an enlarged fontanelle | 0 | 0 | 0 | 1(1) |
| Agenesis of 3 claws (left hindpaw) and of 1 claw (rt. hindpaw) | 0 | 0 | 0 | 1(1) |

[a] = some observations may be grouped together
[b] = fetal (litter) incidence

An increase in frank malformations including peromelia in 5 fetuses/4 litters, palatoschisis in 1 fetus/1 litter, agenesis of the claws of the hindpaw in 1 fetus/1 litter and malrotation of the right hindlimb in 1 fetus/1 litter with hydrocephalus internus was observed in does treated with 100 mg/kg/day. No malformations were observed in any other dose group. Historical control data (control; inactive treatment) from 1984-1986 are presented below (pgs. 127-136):

| | 1984 | 1985 | 1986 |
|---|---|---|---|
| Peromelia | 0 | 0 | 0 |
| Palatoschisis | 0 | 0 | 0 |
| Malrotation of hindlimb | 0 | 1/860(.05%) | 2/2146(.09%) |
| Hydrocephalus internus | 1/886(.1%) | 0 | 1/2146(.05%) |
| Agenesis of claws | 0 | 0 | 0 |

Based upon the lack of similar malformations in the controls and the significantly lower incidence of malrotation of the hindlimb and hydrocephalus internus and the lack of occurrence of peromelia, palatoschisis and agenesis of the claws in the historical control data, the findings are considered compound-related.

Visceral Examinations

No abnormal findings were noted.

Skeletal Examinations

Skeletal findings are presented below in Table VI. There was a small but consistent effect of terbuconazole upon the rate of ossification as well as a more general finding simply stated as various bones in the HDT as compared to the control group. Specific fetal findings included increased nonossification of digit 5 medial phalanx (left forelimb), incomplete ossification of digit 2 proximal phalanx (right forelimb) and digits 2, 4 medial phalanx (right forelimb), and increased nonossification of left and right hindlimb (toe 4 medial phalanx).

D. DISCUSSION/CONCLUSION

a. Maternal toxicity:

Oral administration of terbuconazole at 0, 10, 30 and 100 mg/kg/day during days 6-18 of gestation in the Chinchilla rabbit produced a minimal depression in mean body weight gain at the HDT associated with a decrease in food consumption. No other significant effects were noted in regards to clinical signs, organ weights or gross necropsy findings.

b. Developmental toxicity:

The mean number of live fetuses/dam were reduced in the HDT as compared to the controls due to an increase in postimplantation losses (both early and late resorptions). Small decreases in the rate of ossification were noted in HDT fetuses in the right and left digits or toes of the fore- and hindlimb. Frank malformations in 8 fetuses of 5 litters (peromelia, palatoschisis, malrotation of right hindlimb, agenesis of claws) were noted in the HDT but not in concurrent controls or at the same frequency in historical data. These effects are considered compound-related.

c.

No significant study deficiencies were noted. However, it is unclear to the reviewer what the investigators mean when they record the skeletal finding of "various bones", and it is requested that this finding be clarified. This is not critical to a determination regarding the NOEL for developmental effects.

E. CLASSIFICATION: CORE MINIMUM DATA.

Maternal NOEL = 30 mg/kg/day
Maternal LOEL = 100 mg/kg/day
Developmental Toxicity NOEL = 30 mg/kg/day
Developmental Toxicity LOEL = 100 mg/kg/day

F. RISK ASSESSMENT:

Development of MOS has been determined to be unnecessary at this time.

Skeletal Examinations

Table VI: Skeletal Examinations

| Observations[a] | Control | LDT | MDT | HDT |
|---|---|---|---|---|
| # pups(litters) examined | 111(15) | 113(14) | 127(15) | 90(14) |
| VARIOUS BONES | | | | |
| Total litters affected | 0 | 1 | 2 | 4 |
| Number of fetuses(%): | 0 | 1 | 2 | 6 |
| LEFT FORELIMBS (Nonossified) | | | | |
| Total litters affected | 14 | 14 | 15 | 14 |
| Number of fetuses(%): | | | | |
| Digit 5 medial phalanx | 80(72) | 84(74) | 90(74) | 78(87) |
| RIGHT FORELIMB (Incompletely ossified) | | | | |
| Total litters affected | 8 | 10 | 11 | 9 |
| Number of fetuses(%): | | | | |
| Digit 1 proximal phalanx | 6(5) | 7(6) | 4(3) | 13(14) |
| Digit 2 medial phalanx | 2(2) | 3(3) | 2(2) | 5(6) |
| Digit 4 medial phalanx | 16(14) | 19(17) | 26(21) | 21(23) |
| LEFT HINDLIMB (Nonossified) | | | | |
| Total litters affected | 9 | 10 | 9 | 10 |
| Number of fetuses(%): | | | | |
| Toe 4 Medial Phalanx | 17(15) | 22(19) | 23(19) | 36(40) |
| RIGHT HINDLIMB (Nonossified) | | | | |
| Total litters affected | 8 | 10 | 8 | 11 |
| Number of fetuses(%): | | | | |
| Toe 4 Medial Phalanx | 16(14) | 21(19) | 22(18) | 35(39) |

Appendix 9. Rat 2-Generation Reproduction Study.

Appendix 9. Rat 2-Generation Reproduction Study.

Reviewed by: James N. Rowe, Ph.D., James N. Rowe 12/23/88
Review Section I
Tox. Branch-Herb./Fung./Antimicrobial Support (TS-769C)
Secondary reviewer: Quang Q. Bui, Ph.D.
Review Section I, Tox. Branch-H./F./A.S. (TS-769C) Quang Q Bui 12/23/88

DATA EVALUATION REPORT

STUDY TYPE: Two generation rat reproduction, EPA Guideline 83-4

TOX. CHEM. NO.: 463P

ACCESSION NUMBER: MRID NO.: 407009-46

TEST MATERIAL: HWG 1608 TECHNICAL; mixed batch no. F1. no. 132; whitish-beige powder; purity of 95.2%; refrigerated during the study

SYNONYMS: ethyl-trianol; 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazole-1-yl-methyl)pentane-3-ol

STUDY NUMBER(S): report no. 16223; Lab. proj. ID no. 91064; study no. T 5017647

SPONSOR: MOBAY Corporation, Agricultural Chemicals Division

TESTING FACILITY: Toxicology Division, Bayer AG, Wuppertal, Friedrich-Ebert-Str. 217-333 and PATCO AG, CH-4452 Itingen, Switzerland

TITLE OF REPORT: HWG 1608, Two-generation study in rats

AUTHOR(S): Dr. R. Eiben (study director)

REPORT ISSUED: November 12, 1987

QUALITY ASSURANCE/GLP/CONFIDENTIALITY:

Signed copies of no confidentiality, GLP statement and quality assurance were included.

CONCLUSIONS:

Dietary administration of terbuconazole at dosages of 0, 100, 300 and 1000 ppm to male and female Wistar rats resulted in parental toxicity primarily at the HDT expressed as increased clinical signs of toxicity (loss of hair), depressed body weights, increased severity of spleen hemosiderosis (females only) and decreased liver and kidney weights in both F0 and F1B males and/or females. Decreased pup viability was observed in F0 but not F1B neonates while there was a significant depression in pup body weight of all littering groups (F1a, F1b, F2a, F2b) at the HDT from birth on. A systemic toxicity LOEL ( based upon depressed body weights, increased clinical signs of toxicity,

decreased food consumption, increased spleen hemosiderosis and decreased liver and kidney weights) is set at 1000 ppm and a NOEL is set at 300 ppm. The reproductive LOEL, based upon neonatal birth weight depression, is set at 1000 ppm and the NOEL is set at 300 ppm.

CORE: Minimum

MATERIALS AND METHODS:
(A photocopy of the materials and methods is appended)

1. Dosage

SPF-bred Wistar rats (strain Bor: WISW (SPF Cpb); from Winkelmann, Borchen) were divided into four study groups (25 of each sex/dose group) and given terbuconazole weekly in the diet at 0, 100, 300 and 1000 ppm (control,LDT, MDT, HDT, respectively) throughout the study, including mating period, gestation and pup lactation (total exposure period of approximately 40 weeks). Specific exposure periods for individual study sections are given in appended methods.

2. Experimental Plan (see methods for time sequence, p. 19)

Each FO female was housed singly until about 17 weeks of age and then mated with one male. Rats (1 female/1 male) were kept in one cage during the mating period with the date of insemination determined by vaginal smears or the presence of vaginal plugs. The calculation of the gestation period was based upon the date of sperm finding, as day 0 of gestation. Five days after birth, the litters were reduced, if necessary, to 8 animals. Animals for further treatment were randomly selected. Pups in the F1a generation (and F2a) were reared and then sacrificed at four weeks. After two week waiting periods, the FO parental animals were mated a second time. The F1b pups were kept and reared for four weeks, like the pups from the first mating, and then separated from the dams. Four week old F1B (F1b) pups were selected for further treatment and matings.

After reaching an average age of 100 days, F1B parental first matings were performed (20 day period) with a 3 week gestation period. F2a pups were kept for a 6 week period and a second mating and gestation period was observed (F2b; 6 weeks duration). Males in the FO and F1B generations were sacrificed after the last mating. F2b pups were reared up to three weeks of age and then sacrificed. Note: FO rats which had not been fertilized twice were additionally mated with fertile males in the same group and the resulting generation was termed F1C (pg. 16), a somewhat misleading term since all rats must be remated after the first pregnancy anyway. These rematings gave no significant additional data.

3. Necropsy of Adults and Pups

The rats which died or sacrificed moribund during the study were dissected and grossly examined. All the FO and F1B parents were sacrificed about one to three weeks after the pups were weaned, dissected and grossly examined. The brain, pituitary, liver, kidney, adrenals, testicles, epididymis, seminal vesicle, prostate, ovaries, uterus, vagina, spleen, mammary glands (females only) and organs with gross alterations were fixed.

F1B parents' livers, spleens, kidneys, adrenals and testicles or ovaries (pairwise) were weighed.

At an age of about 4 weeks, all the F1B which had not been selected, and all the F2B pups (age 3 weeks) were sacrificed and grossly examined with special attention paid to the reproductive organs. The pups which died were not necropsied since they were autolytic and/or could not be appraised due to cannibalism.

4. Bone examination of F1B rats

The right rear femur of all F1B male rats were removed after necropsy and measured for length and diameter at the thinnest point. The bone was fixed in 10% formaldehyde. No reason for examination of only male femurs was given.

5. Statistics

Arithmetic group means, standard deviations and upper and lower confidence limits were determined. The test collective values were compared with the controls by the U test of Mann and Whitney and Wilcoxon. For indices (formed from magnitudes) the confidence limits were calculated by Clopper and Pearson's method.

Test collective indices were compared with controls by Fisher's Exact test (significance of $p<0.5$ or 0.01). Random lists were produced with the aid of a Subprogram Randu from IBM.

RESULTS:

1. Mortality/clinical signs

Five females died or were sacrificed moribund during the test period (2 females/0 ppm (#s 38, 40+), after first mating; 1 female/1000 ppm (#185), after second mating; 1 female/0 ppm (#237+), during lactation, F2A generation; 1 female/1000 ppm (#387), after birth of F2b pups). These were not dose-related effects.

A summary of the major clinical signs is presented below:

| CLINICAL SIGN*: | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| F0 adults | m | f | m | f | m | f | m | f |
| Loss of hair | 55 | 123 | 0 | 92 | 24 | 81 | 21 | 196 |
| Inflammation/changes of the eye | 0 | 2 | 3 | 0 | 0 | 0 | 19 | 0 |
| F1B adults | | | | | | | | |
| Loss of hair | 22 | 39 | 0 | 35 | 39 | 63 | 36 | 72 |
| Inflammation/changes of the eye | 0 | 15 | 0 | 9 | 0 | 0 | 0 | 0 |
| Ill/bad condition | 3 | 1 | 1 | 0 | 0 | 0 | 8 | 0 |

* total number of observations reported

There was a general increase in the reported incidence of toxicity signs at the high dose for loss of hair in F0 females (HDT/196 days vs Control/123 days). For inflammation of the eyes, treated F0 males appeared elevated over control values (HDT/19 vs Control/2) but control females had a greater incidence then HDT females( control/15 days vs HDT/0 days). This suggests that a treatment related effect for eye inflammation is questionable. The incidence of loss of hair in F1B females was also increased at the HDT and MDT (HDT/72 days, MDT/63 days vs Control/39 days) and possibly an increase in the observation of ill/bad condition for HDT F1B males (HDT/8 days vs Control/3 days).

2. Body weights/food consumption data

Mean body weights for the F0 and F1B adults are presented below:

| Week on study | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| F0 males: | | | | |
| 0 | 92(7)[b] | 92(7) | 93(7) | 91(7) |
| 1 | 131(8) | 129(10) | 130(9) | 118(9)* |
| 17 | 351(25) | 343(22) | 348(24) | 327(23)** |
| 29 | 374(23) | 370(26) | 370(25) | 354(26)** |
| 34 | 380(24) | 381(25) | 380(25) | 364(25)** |
| F0 females: | | | | |
| 0 | 88(5) | 89(5) | 90(6) | 89(6) |
| 1 | 110(6) | 111(8) | 111(7) | 104(7)** |
| 17 | 206(14) | 208(17) | 206(16) | 196(17)* |
| d6[a] | 218(15) | 223(17) | 219(18) | 208(17)* |
| d20 | 284(24) | 282(33) | 288(36) | 263(35)* |
| 29 | 223(15) | 224(19) | 222(19) | 209(20)* |
| d6 | 234(17) | 240(22) | 233(21) | 218(23)* |
| d20 | 311(34) | 293(37) | 286(46) | 284(41)* |
| 34 | 263(15) | 255(25) | 249(25) | 233(25)** |
| F1B males: | | | | |
| 5 | 97(11) | 92(12) | 99(12) | 82(16)** |
| 14 | 317(36) | 317(35) | 321(27) | 286(32)** |
| 27 | 390(35) | 388(36) | 381(32) | 352(41)** |
| 31 | 390(35) | 391(36) | 390(34) | 356(42)** |
| F1B females: | | | | |
| 5 | 86(7) | 83(8) | 89(7) | 75(14)** |
| 14 | 192(14) | 192(16) | 195(13) | 180(17)** |
| d6 | 211(18) | 214(16) | 216(15) | 199(19)* |
| d20 | 278(33) | 286(31) | 290(26) | 265(32) |
| 27 | 219(15) | 222(17) | 224(14) | 206(17)** |
| d6 | 238(20) | 237(17) | 243(16) | 223(19)* |
| d20 | 298(35) | 302(45) | 314(36) | 278(32)* |
| 32 | 247(28) | 242(18) | 244(17) | 225(20)** |

[a] d = days after female insemination; [b] mean in grams (standard deviation)(data taken from pp. 53-58 of report)

Mean body weights were consistently depressed in both male and female adult rats exposed to tebuconazole at 1000 ppm prior to mating, after mating, during lactation and following the lactation period in both the F0 and F1B parental generations.

Summary food consumption data (g/animal/day) are presented below:

| Week on study FO(male/female) | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| 1 | 15.09/13.54 | 15.07/13.73 | 14.89/14.23 | 13.73/13.21 |
| 5 | 20.16/14.80 | 19.28/15.18 | 21.27/15.15 | 19.18/14.98 |
| 10 | 21.23/15.43 | 20.77/16.41 | 21.57/16.04 | 20.93/16.42 |
| 17 | 21.15/16.08 | 19.95/20.76 | 19.60/22.10 | 19.17/16.27 |
| Entire period (W1-W17) | 21/15 | 20/16 | 20/16 | 19/16 |
| F1B(male/female) | | | | |
| 6 | 16.98/15.81 | 16.41/14.54 | 16.04/13.19 | 14.83/13.33 |
| 10 | 25.00/18.47 | 24.46/19.31 | 25.39/20.31 | 23.94/18.75 |
| 15 | 24.58/18.90 | 23.88/17.31 | 24.70/18.37 | 22.23/15.99 |
| Entire period (W6-W15) | 24/19 | 24/18 | 24/19 | 22/17 |

(food data up to first mating; FO = pgs. 78, 79; F1B = p. 122)

No statististically significant effects upon food consumption were observed in either parental generation prior to mating. However, there was a small, generally consistent, depression observed in the 1000 ppm males and/or females of both the F0 and F1B parents over the entire measurement period (FO: males/10%; F1B: males/8%, females/11%) as compared to the respective controls.

3. Reproductive indices

A summary table of reproductive indices is presented below. The fertility index ranged from 75% to 96% and fluctuated considerably but did not appear to be a dose-related effect in either the F0 or F1B generations. The insemination index, gestation index or mean gestation period were not different among the dose groups in either generation. There were statistically significant depressions in the viability index of the F0 generations in the F1a males at 100 and 1000 ppm ( 90.3%, 88.1%, respectively vs 98.5%/control) and in the lactation index male and/or females of F1a or F1b animals at 100 and 1000 ppm (F1b: 76.1%/females vs 90.9% control; F1a, F1b, resp.: 86.3%, 80.3% vs 95.2%, 90.9%/controls). However, in the F1B generation, neither the F2a or F2b litters were affected in a compound-related manner.

F0 generations

| Dose: | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| Parameters | F1a | F1b | F1a | F1b | F1a | F1b | F1a | F1b |
| # females | 25 | 23 | 25 | 25 | 25 | 25 | 25 | 25 |
| insemination index | 100 | 100 | 96.0 | 92.0 | 100 | 96.0 | 96.0 | 92.0 |
| gestation index | 100 | 100 | 100 | 94.4 | 100 | 100 | 90.5 | 95.5 |
| gesta. period(d) | 22.3 | 22.0 | 22.2 | 21.9 | 22.3 | 22.2 | 22.3 | 22.1 |
| fertility index | 88.0 | 95.7 | 75.0 | 78.3 | 88.0 | 75.0 | 87.5 | 95.7 |
| viability index | 98.5 | 94.5 | 90.3** | 89.4 | 95.2 | 94.2 | 88.1** | 88.5 |
| lactation index | 95.2 | 90.9 | 88.9 | 76.1** | 91.1 | 98.2* | 86.3* | 80.3* |
| # viable ltrs | 22 | 22 | 17 | 17 | 18 | 18 | 19 | 21 |
| # nonviable ltrs | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 |

F1B generations

| Dose: | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| Parameters | F2a | F2b | F2a | F2b | F2a | F2b | F2a | F2b |
| # females | 25 | 24 | 25 | 25 | 25 | 25 | 25 | 25 |
| insemination index | 100 | 100 | 100 | 100 | 96.0 | 100 | 100 | 100 |
| gestation index | 100 | 91.3 | 100 | 100 | 100 | 100 | 100 | 100 |
| gesta. period(d) | 22.3 | 22.1 | 22.0 | 21.7 | 22.1 | 21.7 | 22.0 | 22.1 |
| fertility index | 96.0 | 95.8 | 96.0 | 84.0 | 95.8 | 92.0 | 92.0 | 84.0 |
| viability index | 98.0 | 91.7 | 99.6 | 96.0 | 97.7 | 98.9** | 96.6 | 91.1 |
| lactation index | 98.4 | 97.3 | 99.5 | 97.0 | 99.5 | 97.2 | 97.2 | 97.9 |
| # viable ltrs | 24 | 21 | 24 | 21 | 23 | 23 | 23 | 21 |
| # nonviable ltrs | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

(Definitions of parameters:

Fertility index = $\frac{\text{number of pregnant females x 100}}{\text{number of mated females}}$

Gestation index = $\frac{\text{number females with live litters x 100}}{\text{number of pregnant females}}$

Viability index = $\frac{\text{number live pups after 5 days x 100}}{\text{number pups born alive}}$

Lactation index = $\frac{\text{number of live pups after 4 weeks x 100}}{\text{number of live pups after 5 days after reduction}}$

Insemination index = $\frac{\text{number of mated females x 100}}{\text{number paired females}}$

4. Neonatal indices (from pp. 60-63, 70-73 of report)

FO: F1a

| Dose: | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| total # | 204 | 186 | 225 | 177 |
| # dead | 5 | 0 | 16 | 17 |
| #/litter(d0) | 9.0(1.7) | 10.3(2.9)* | 9.5(2.8) | 7.6(3.4) |
| #/litter(5DBR) | 8.9(0.8) | 9.3(2.7) | 9.0(3.1) | 6.7(3.7) |
| #/litter(5DAR) | 7.6(0.7) | 7.5(1.7) | 7.2(1.9) | 5.9(3.0) |
| #/litter(Wk 1) | 7.4(1.3) | 7.4(1.7) | 6.9(2.2) | 5.8(3.1) |
| #/litter(Wk 4) | 7.2(1.8) | 6.7(2.4) | 6.5(2.2) | 5.1(3.3)* |
| % males | 48 | 51 | 47 | 51 |
| Pup wt.(birth) | 6.0(0.5) | 5.7(0.5)* | 5.8(0.6) | 5.6(0.4)* |
| Pup wt.(5DBR) | 10.2(1.2) | 9.4(1.0) | 9.8(1.5) | 9.0(1.4)** |
| Pup wt.(5DAR) | 10.4(1.2) | 9.6(1.0) | 10.0(1.4) | 9.0(1.4)** |
| Pup wt. (Wk 1) | 12.6(1.9) | 12.4(1.6) | 13.2(2.2) | 10.7(2.2)** |
| Pup wt. (Wk 4) | 54.1(5.1) | 53.7(5.3) | 56.6(7.5) | 47.8(8.0)** |

FO: F1b

| | | | | |
|---|---|---|---|---|
| total # | 210 | 159 | 151 | 160 |
| # dead | 9 | 8 | 12 | 12 |
| #/litter(d0) | 9.1(2.1) | 8.4(3.6) | 7.7(3.4) | 6.7(3.3)* |
| #/litter(5DBR) | 8.6(2.3) | 7.5(3.3) | 7.3(3.5) | 6.0(3.7)* |
| #/litter(5DAR) | 7.5(1.0) | 6.5(2.3) | 6.3(2.5) | 5.3(3.0)** |
| #/litter(Wk 1) | 7.4(1.0) | 6.1(2.6) | 6.3(2.5) | 4.9(3.0)** |
| #/litter(Wk 4) | 6.8(1.7) | 4.9(2.9)* | 6.2(2.5) | 4.3(3.0)** |
| % males | 50 | 49 | 47 | 51 |
| Pup wt.(birth) | 5.7(0.5) | 5.6(0.7) | 5.7(0.6) | 5.6(0.8) |
| Pup wt.(5DBR) | 9.3(1.2) | 8.5(1.6) | 10.2(1.9) | 8.9(1.9) |
| Pup wt.(5DAR) | 9.4(1.2) | 8.5(1.6) | 10.3(1.9) | 8.8(1.9) |
| Pup wt. (Wk 1) | 12.7(1.6) | 11.2(2.6) | 13.6(2.1) | 11.4(2.7)* |
| Pup wt. (Wk 4) | 58.7(10.1) | 58.6(8.6) | 60.2(8.8) | 52.4(8.8) |

F1B: F2a

| | | | | |
|---|---|---|---|---|
| total # | 255 | 271 | 261 | 239 |
| # dead | 3 | 3 | 3 | 4 |
| #/litter(d0) | 10.5(2.0) | 11.2(1.0) | 11.2(2.1) | 10.2(1.5) |
| #/litter(5DBR) | 10.3(1.9) | 11.1(1.0) | 11.0(2.1) | 9.9(1.4) |
| #/litter(5DAR) | 7.9(0.6) | 8.0(0.0) | 7.9(0.3) | 7.9(0.5) |
| #/litter(Wk 1) | 7.8(0.6) | 8.0(0.0) | 7.9(0.3) | 7.8(0.5) |
| #/litter(Wk 4) | 7.7(0.7) | 8.0(0.2) | 7.9(0.3) | 7.7(0.8) |
| % males | 48 | 45 | 49 | 49 |
| Pup wt.(birth) | 5.9(0.6) | 5.5(0.3)** | 5.7(0.5) | 5.3(0.3)** |
| Pup wt.(5DBR) | 9.9(1.5) | 9.3(0.8) | 9.6(1.2) | 8.1(1.0)** |
| Pup wt.(5DAR) | 10.1(1.5) | 9.4(0.8)* | 9.7(1.2) | 8.1(0.9)** |
| Pup wt. (Wk 1) | 12.7(1.9) | 12.1(1.3) | 12.6(1.9) | 10.3(1.2)** |
| Pup wt. (Wk 4) | 56.0(6.1) | 56.4(4.2) | 56.4(5.6) | 43.7(5.0)** |

(continued from previous page

F1B: F2b

| Dose: | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| total # | 214 | 253 | 273 | 213 |
| # dead | 8 | 5 | 11 | 10 |
| #/litter(d0) | 9.0(3.9) | 11.8(2.3)** | 11.4(2.4)* | 9.7(3.3) |
| #/litter(5DBR) | 8.2(4.0) | 11.3(2.0)** | 11.3(2.4)** | 8.8(3.9) |
| #/litter(5DAR) | 6.5(2.7) | 7.9(0.7) | 7.9(0.6) | 6.8(2.5) |
| #/litter(Wk 1) | 6.5(2.8) | 7.9(0.7) | 7.9(0.6) | 6.8(2.5) |
| #/litter(Wk 4) | 6.3(2.9) | 7.6(1.2) | 7.7(0.7) | 6.7(2.5) |
| % males | 45 | 43 | 50 | 51 |
| Pup wt.(birth) | 5.7(0.6) | 5.7(0.3) | 5.7(0.4) | 5.3(0.5)* |
| Pup wt.(5DBR) | 9.2(1.5) | 9.1(0.9) | 9.4(1.1) | 8.4(2.7)** |
| Pup wt.(5DAR) | 9.3(1.5) | 9.3(0.8) | 9.7(1.2) | 8.5(2.6)** |
| Pup wt. (Wk 1) | 12.6(2.0) | 12.0(1.3) | 12.6(1.7) | 10.0(1.1)** |
| Pup wt. (Wk 3) | 36.0(4.2) | 36.8(4.2) | 38.1(3.0) | 30.5(3.4)** |

5 DBR = day 5, before reduction; 5 = DAR, after reduction; wk = week after birth

Summary tables of neonatal indices are presented above. There was a significant number of dead fetuses observed in the mid and high dose groups of the F1a litter as compared to the controls (5/control vs 16 or 17, respectively) as well as a smaller increase in both dose groups in the F1b littering group (9/control vs 12/MDT, 12/HDT). No consistent increase in number of dead fetuses was observed in the F1B generation. A statistically significant decrease in the mean number fetuses/litter at birth through week four of lactation was observed in both litters of the F0 generation at the HDT (e.g., at week four, statistically significant decrease: 5.1/dam vs 7.2/dam, F1a; 4.3/dam vs 6.8/dam, F1b) as compared to the control values. However, this was not observed in either the F2a or F2b litters of the F1B generation either at birth or at the end of the lactation period. This significant decrease was observed only after the reduction (day 5) in the F1a pup but <u>both</u> before and after culling of F1b pups suggesting fetal toxicity at parturition with continued fetal toxicity through weaning. Neonatal weights from birth through weeks 3 or 4 of lactation were consistently and statistically significantly depressed in both the F0 and F1B generations in all littering groups (F1a, F1b, F2a, F2b) at the HDT and is considered to be a compound-related effect.

5. Gross necropsy/histopathology

a. Gross necropsy

No apparent compound-related gross changes were observed in parental animals.

b. Histopathology

Selected histopathology findings are presented below (taken from pages 241C-243C):

Organ/Finding

| | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| F0 adults | m | f | m | f | m | f | m | f |
| KIDNEYS: # exam. | 25 | 24 | 25 | 25 | 25 | 25 | 25 | 25 |
| -lymphoid c. infiltr. | 2 | 3 | 9 | 7 | 4 | 7 | 12 | 4 |
| -tubular atrophy | 18 | 6 | 17 | 10 | 24 | 9 | 21 | 9 |
| TESTES: # exam. | 25 | | 25 | | 25 | | 25 | |
| -tubular atrophy | - | | 1 | | 2 | | 2 | |
| -Leydig c. hyperplasia | - | | - | | 1 | | - | |
| OVARIES: # exam. | | 25 | | 25 | | 25 | | 25 |
| -cysts(s) | | 2 | | 4 | | 5 | | 3 |
| SPLEEN: # exam. | 24 | 24 | 25 | 25 | 25 | 25 | 24 | 25 |
| -hemosiderosis | 22 | 23 | 25 | 24 | 25 | 25 | 24 | 25 |
| -hemopoiesis | 10 | 8 | 14 | 10 | 8 | 14 | 17 | 5 |
| F1B adults | m | f | m | f | m | f | m | f |
| KIDNEYS: # exam. | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| -tubular atrophy | 20 | 5 | 21 | 10 | 18 | 5 | 20 | 7 |
| OVARIES: # exam. | | 24 | | 25 | | 25 | | 25 |
| -cysts(s) | | 1 | | 2 | | 1 | | 3 |
| SPLEEN: # exam. | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| -hemosiderosis | - | 1 | - | - | - | - | - | 9 |

---

HEMOSIDEROSIS (SEVERITY)

| | 0 ppm | | 100 ppm | | 300 ppm | | 1000 ppm | |
|---|---|---|---|---|---|---|---|---|
| FO ADULTS | m | f | m | f | m | f | m | f |
| -grade 2 | 9 | 11 | 10 | 7 | 7 | 5 | 3 | 0 |
| -grade 3 | 13 | 11 | 15 | 14 | 17 | 14 | 21 | 6 |
| -grade 4 | 0 | 1 | 0 | 3 | 0 | 4 | 0 | 19 |
| F1B ADULTS | | | | | | | | |
| -grade 3 | 0 | 1 | ------ | | ------ | | 0 | 9 |

There appears to be a possible elevation in the finding of lymphoid cell infiltration in F0 males in the HDT (12 vs 2/control) but this was not observed in F1B males. An increase in tubular atrophy was apparent in F1B males at the HDT (20 vs 5/control) but not in F0 males. These findings are therefore discounted.

Hemosiderosis of the spleen appears to be a compound-related toxicity. The incidence in F0 males and females is close to 100% but confined to only the control and HDT females of the F1B generation at a much lower incidence rate. However, from examination of the severity (grade) of the lesions it is evident that HDT F0 females (grade 4: 19 vs 1/control) and HDT F1B females (grade 3: 9 vs 1/control) had elevated findings as compared to controls.

6. Organ weights(mg)/organ-to-body-weight ratios (mg/100 gm)

Selected organ weights/organ-to-body-weight ratios for F1B adults are presented below:

| F1B males | 0 ppm | 100 ppm | 300 ppm | 1000 ppm |
|---|---|---|---|---|
| Body wt.(gm) | 390 | 391 | 390 | 356** |
| Liver | 13694/3512 | 13898/3546 | 12613/3230** | 12071**/3383 |
| Kidney | 2391/613 | 2360/603* | 2408/617 | 2144**/604 |
| Adrenal | 44/11 | 42/11 | 40/10* | 39*/11 |
| Testes | 3804/978 | 3879/996 | 3793/974 | 3729/1057** |
| **F1B females** | | | | |
| Body wt.(gm) | 237 | 238 | 241 | 224* |
| Liver | 9402/3960 | 9485/3988 | 9923/4110 | 9196/4110 |
| Kidney | 1576/666 | 1554/652 | 1612/667 | 1458*/651 |
| Ovaries | 147/62 | 149/63 | 155/64 | 146/65 |

*, ** statistically significantly different from controls ($p<0.05$, 0.01, respectively)

Mean liver weights (mg)and liver to body weight ratios (%) were decreased in F1B males but not females at the mid and high dose levels, respectively (e.g., males: mid, 12613/3230** vs control, 13694/3512; females: high, 9196/4110 vs control, 9402/3960; $P<0.01$). Kidney weights as well as organ to body weight ratios were also somewhat lower at the HDT as compared to the controls

in both male and female rats (absolute weights statistically significant, e.g., . males: mid, 2144**/604 vs 2391/613). No consistent findings were evident for male adrenals or testes. Female ovary weights were not altered.

7. Bone examination

A summary data table of right femurs from F1B males is presented below:

| Dose(ppm) | length (cm) | diameter (mm) |
|---|---|---|
| 0 | 3.65 | 4.38 |
| 100 | 3.64 | 4.55 |
| 300 | 3.62 | 4.46 |
| 1000 | 3.59 | 4.50 |

There was no effect of terbuconazole on bone growth of the right femurs from F1B males.

SUMMARY/CONCLUSIONS:

Administration of terbuconazole continuously in the diet of male and female Wistar rats at 0, 100, 300 and 1000 ppm prior to mating, during mating and gestation and lactation produced evidence of parental toxicity, primarily at the high dosage level. There was an increase in the incidence of hair loss in MDT and HDT females (F0, F1B). Mean body weights were depressed in both HDT males and females of both generations and were associated with a small depression in food consumption (primarily in females). HDT females of both generations had an increase in the severity of hemosiderosis of the spleen. Absolute and relative liver and kidney weights were depressed in F1B (primarily HDT) males and/or females.

Inconsistent reproductive effects were observed between the F0 and F1B generations. In the F0 generation, there was a statistically significant decrease in fetal viability based upon a decrease in the mean viability index at 100 and 1000 ppm in F1a males and in the lactation index of male and/or females of F1a and F1b litters at 100 or 1000 ppm. No alteration was observed in the F1B litters. This was reflected in the F0 litters by the decrease in the mean pup counts/litter observed in both F1a and F1b at birth through the end of weaning. No such findings were reported for the F1B litters. These findings may be accounted in part by the considerable variability in the fertility rate observed in the F0 generation. It may also be a result of acclimation of the parental animals to the toxicant (long-term stimulation of liver microsomal enzymes resulting in accelerated detoxification patterns in the F1B litters; terbuconazole is known to stimulate increased liver microsoma metabolism).

A consistent, statistically significant depression in neonatal weights from birth through lactation (week 3 or 4) was observed in all littering groups of F0 and F1B at the HDT. This is considered an unequivocal compound-related effect upon the pups which may be a post-natal expression of reproductive toxicity (retarded neonatal growth) since it is seen at birth and continues onward through the weaning period. However, it should be noted that there was no indication of growth retardation based upon bone formation in the right femurs of F1B males.

Appendix 10. 1-Liners for Developmental Toxicity Studies (Analogues).

TOXCHEM NO. 862AA- 1-[1,2,4-Triazoyl-1]-1-[4-chloro-phenoxy]-3,3-dimethyl-butanone FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>St. Marianna Univ.; Japan<br>As81-3014; 3/13/81 | Bayleton Tech 99% | 070570<br>070569 | Teratogenic NOEL = 50 mg/kg/day. Teratogenic LEL = 100 mg/kg/day (Cleft Palates). Maternal Toxic NOEL = 10 mg/kg/day Maternal Toxic LEL = 25 mg/kg/day. (increased motor activity and/or depression of maternal weight gain) | | Minimum<br>001533 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>6294; 8/27/76 | Bayleton Tech in 0.5% aq. Cremphor Emulsion | | Maternal NOEL = 10 mg/kg. Maternal LEL = 30 mg/kg (Decreased weight gain). Teratogenic NOEL = 50 mg/kg Teratogenic LEL = 75 mg/kg (cleft palate) Levels tested = 0, 10, 30, 75, 100 mg/kg/day. | | Minimum<br>002005 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>6298; 8/30/76 | Bayleton Tech. | | Teratogenic NOEL > 113.66 mg/m3/6hr. Maternal NOEL > 113.66 mg/m3/6 hrs. (Highest level tested) for 10 days. Levels tested = 0, 14.03, 33.2, 113.66 mg/m3 | | Minimum<br>002003 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Midwest Research Inst.<br>7272-8; 8/31/82 | Bayleton 93.2% | 254697 | Maternal NOEL = 30 mg/kg , Maternal LEL = 90 mg/kg . These values are based on a statistically significant (P < 0.05) decrease in body weight gain during the dosing period of the 90 mg/kg dams . A non-statistically significant increase in late fetal resorptions was also found in this group . No maternal toxicity was observed in the 30 mg/kg treatment group . Developmental NOEL = 30 mg/kg , Developmental LEL = 90 mg/kg . These values are based on a statistically significant (P > 0.05) increase in abnormal ribs, especially extra ribs , in fetuses from the 90 mg/kg treated dams . A statistically significant (p <0.05) increase in distended urinary bladders was also observed in these fetuses . No developmental toxicity was observed at the 30 mg/kg dose level. Levels tested in CD-SD strain: 0, 10, 30 and 90 mg/kg by gavage. | | Supplementary<br>006841 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>6297; 8/30/76 | Bayleton Tech. | | Teratogenic NOEL > 50 mg/kg(HDT). Maternal NOEL > 50 mg/kg (HDT) Levels tested = 5, 15, 50 mg/kg | | Minimum<br>002003 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>T30C-3938; 4/21/82 | Bayleton 93.5% | 254697 | Maternal NOEL = 10 mg/kg, Maternal LEL = 30 mg/kg. These values are based on a marked decrease in mean weight gain during the treatment period and also for the entire gestational period in the 30 mg/kg group. While these decreases were not statistically significant (P< 0.01) at the 100 mg/kg level. Developmental NOEL =30 mg/kg, Developmental LEL = 100 mg/kg. These values are based on a statistically significant increase in the number of fetal resorptions in the 100 mg/kg group. No developmental toxicity was observed at the 30 mg/kg dose level. Levels tested in Himalayan strain: 0, 10, 30, and 100 . | | Supplementary<br>006841 |

192

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS



TOXCHEM NO. 862AA- 1-[1,2,4-Triazoyl-1]-1-[4-chloro-phenoxy]-3,3-dimethyl-butanone FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Miles Laboratories<br>MTD0149; 3/22/90 | Triadimefon tech., 94.3% a.i. | 414462-01 | Maternal NOEL = 50 mg/kg/day (MDT). Maternal LOEL = 120 mg/kg/d (MDT), based on a marginal body weight loss (80 gm; day 6-10).<br>Developmental NOEL = 20 mg/kg/day (LDT). Developmental LOEL = 50 mg/kg/d based on dose-related (MDT & MDT) increases in incidences of incomplete ossification of pelvic pubes, anterior phalanges, posterior phalanges, and of irregular spinous processes.<br>Other developmental effects at the MDT: decrease in female fetal body weight and placental weight, increases in incid. of rudimentary/missing tails, extra ribs, caudal vertebral arches/centra malformations, incomplete ossification of 1st, 2nd, and 5th sternebrae, posterior talus, and posterior phalanges.<br>Levels tested: 0, 20, 50, and 120 mg/kg/day (oral gavage: day 6-18; American Dutch artificially inseminated rabbits).<br>This study may be upgraded to Minimum upon satisfactory submission of data regarding the stability of the test material during the whole dosing period and computation of the litter data. | | Supplementary<br>008467 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Bayer AG Institut. Fur Tox. Germ<br>TB005283; 5/30/84 | Bayleton 92.6%; | 260443<br>071468 | Systemic NOEL < 50 ppm (reduction of body wt. for F1 females in 500 group. Increased absolute & relative ovary wts. of Fo females of same group. Reproductive NOEL: 50 ppm<br>Reproductive LOEL: 1800 ppm. These values are based on statistically significant ($P < 0.01$) reductions in 1800 ppm F1 pups' mean<br>In F2 pups of this high dose group, statistically significant differences found as reduced litter size, reduced viability for days 0-5, & reduced viability for days 5-28 (all $P < 0.01$). Other significant reductions ($P<0.05$) for F2 pups were in birth wt. & lactational wts. No effects which could be related to treatment observed in litter size or viability, birth wt. or malformations in any of 50 ppm treatment pups. | | Supplementary<br>006563 |

143

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 862AA- 1-[1,2,4-Triazoyl-1]-1-[4-chloro-phenoxy]-3,3-dimethyl-butanone FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-4<br>Reproduction-3 generation<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>8297; 4/12/79 | Bayleton tech. 16002/75 | 099412<br>099413<br>071468 | Fetotoxic NOEL = 50 ppm. Fetotoxic LEL = 300 ppm (decreased pup weight gain). Maternal NOEL = 300 ppm<br>Maternal LEL = 1800 ppm (decreased body weight gain,decreased lactation performance). Reproductive NOEL = 300 ppm<br>Reproductive LEL = 1800 ppm. (Decreased fertility Decreased litter size). Levels tested = 0, 50, 300, 1800 ppm<br>F0 generation: One female died (300 ppm). Body weight decreased in females (1800 ppm). Fertility index decreased in second mating (1800 ppm). Litter size decreased (1800 ppm) in first & second mating. During lactation, survival of pups (1800 ppm) was decreased in first (7.1%) and second (27.8% mating), weight gain of pups was decreased (10%) in first mating.<br>F1 generation: One female (50 ppm), and 3 males (control, 50, 1800 ppm) died of bronchopneumomia. Body weights of males and females (1800 ppm) was decreased. Fertility index decreased in first (1/20) and second (0/20) mating (1800 ppm), and in 50 ppm second mating. Weight gain was decreased in second litters (300 ppm). F2 generation: One female died (300 ppm), weight gain of pups was decreased (300 ppm) in second lactation period. No histological lesions in F2b litters. | | Minimum<br>002008<br>Supplementary<br>004695 |
| 82-1(a)<br>Feeding-3 month<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>840a; 11/76 | Bayleton tech. | 232490 | NOEL > 2000 ppm (HDT). Levels tested = 0, 50, 200, 800, 2000 ppm Decreased body weight gain and food consumption at 2000 ppm was attributed to palatability. | | Minimum<br>002005 |
| 82-1(b)<br>Feeding-13 week<br>Species: dog<br>5071 | Bayleton tech. | 232490 | NOEL > 2400 ppm (HDT). Decreased body weight gain and food consumption at 2400 ppm was attributed to palatability.<br>Also noted at 2400 ppm was decreased hematocrit, RBC count and hemoglobin volume. Decreased microsomal induction.<br>Increased SAP. | | Minimum<br>002005 |
| 82-2<br>Dermal-28d<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>6352; 9/13/76 | Bayleton Tech. | 232490 | NOEL > 250 mg/kg (HDT). Levels tested = 0, 50, 250 mg/kg | | Minimum<br>002005 |

194

TRIADEMENOL
(Baytan)

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 074A- Baytan FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(a)<br>Feeding/oncogenic-2 year<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>11009; 1982 | KWG 0519 (Baytan) Tech<br>94.9% | 071468 | Dose levels: 125, 500, and 2000 ppm clinical chemistry findings indicate that the target organ may be the liver. The levels of SGOT and SGPT were consistently higher at 2000 ppm. Systemic NOEL = 125 ppm.<br>Systemic LEL = 500 ppm (increased SGOT and SGPT).<br>Oncogenic NOEL > 2000 ppm (HDT). | | Minimum<br>004695 |
| 83-1(a) and 83-2(b)<br>Feeding/oncogenic-2 year<br>Species: mice<br>Bayer AG Institt. Fur Tox. Germ<br>10855; 4/19/82 | KWG 0519 Tech 95% (Baytan | 071467 | Levels tested in SPF, strain CF1/W74 - 0, 125, 500, and 2000 ppm. Increased liver nodules, enlarged livers, increased liver weights, decreased body weight gain. Time and dose related increase in SAP, SGOP, SGPT activity. Compound-related increase of hepatic adenomas. Increased incidence of hyperplastic nodules in the liver.<br>Systemic NOEL = 125 ppm. Systemic LEL = 500 ppm (blood chemistry). Oncogenic NOEL = 125 ppm.<br>Oncogenic LEL = 500 ppm (hepatic adenomas in the liver of females). | | Minimum<br>004695<br>006772 |
| 83-1(b)<br>Feeding-2 year<br>Species: dog<br>Bayer AG Institt. Fur Tox. Germ<br>12970; 4/10/84 | KWG-0519 (Baytan) tech. | 073427<br>073380 | NOEL < 150 ppm(LDT) (decrease in mean body weight gain).<br>Under the conditions of the study, KWG 0519 produced no specific target organ toxicity when fed to beagle dogs at levels of 150,600, or 2400 ppm in the diet. Although there were significant decreases ($p < 0.05$) in mean body weights in males receiving 150 and 2400 ppm and in females receiving 600 and 2400 ppm, the biological significance of these change- could not be assessed. There were significant ($p < 0.05$) increases in alkaline phosphatase N-demethylase, and cytochrome P-450 in males receiving 2400 ppm and significant increases in N-demethylase in females receiving 600 and 2400 ppm and in cytochrome P-450 in females receiving 2400 ppm when compared to controls. | | Minimum<br>005337 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>7038; 10/7/77 | WG 0519 (Baytan) Batch<br>16001/76 unspec. purity | 071468 | Levels tested by gavage to FB30. Long Evans strain - 0, 10, 30, and 100 mg/kg from day 6 to day 15 of gestation.<br>Teratogenic NOEL > 100 mg/kg (HDT). Maternal NOEL > 100 mg/kg (HDT).<br>Fetotoxic NOEL > 100 mg/kg (HDT). | | Supplementary<br>004695 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>86664; 5/17/84 | KWG 0519 (Baytan) 95.2%<br>Batch 289/290 | 073427 | Levels tested by gavage in BAY:FB 30 strain from day 6 thru 15 of gestation - 0,10, and 30 mg/kg/day. Maternal NOEL = 10 mg/kg/day<br>Maternal LEL = 30 mg/kg/day (decreased body weight gain)<br>Developmental NOEL = insufficient data.<br>Because of deficiencies in the conduct and reporting of this study, such as the omission of individual data for fetal skeletal and visceral examinations we were unable to assess the teratogenic potential of KWG 0519. Therefore, this study is classified Core Invalid. | | Invalid<br>005337 |

# U.S. ENVIRONMENTAL PROTECTION AGENCY
## OFFICE OF PESTICIDES/HED/SACB
## TOX ONELINERS



TOXCHEM NO. 074A- Baytan FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Res. and Consulting Co.; Switz<br>94463; 2/2/87 | Baytan tech. 97% | 40307805<br>403078-04 | Maternal NOEL = 30 mg/kg. Maternal LEL = 60 mg/kg (based on decreased body wt. and food consumption). Developmental NOEL > 30 mg/kg/day could not be determined; additional data required. | | Supplementary<br>006809<br>007290 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>86664; 5/17/84 | KWG 0519 (Baytan) 95.2% | 073427 | The NOEL and LOEL for maternal toxicity in rats were 10 and 30 mg/kg of KWG 0519, respectively, based on significant decreases in body weight gains at 30 mg/kg/day. The NOEL and LOEL for embryo/fetal toxicity and teratogenic effects could not be assessed. Because of deficiencies in the conduct and reporting of this study, such as the omission of individual data for fetal skeletal and visceral examinations we were unable to assess the teratogenic potential of KWG 0519. Therefore, this study is classified Core Invalid. | | Invalid<br>005337 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Miles Laboratories<br>MTD0156 or 100175; 5/8/90 | Baytan Tech. 95% | 414984-01 | Maternal Tox NOEL = 5 mg/kg/day. Maternal LEL = 15 mg/kg/day. Developmental NOEL < 5 mg/kg/day (tentative). Dev. LEL = 5 mg/kg/day. Doses: 5, 15, 25 or 60 mg/kg/day in Charles Ricer Crl:CDBr strin. | | Supplementary<br>008269 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Huntingdon Res. Centre, Eng.<br>494; 4/80 | KWG 0519 (Baytan) Tech. | 071468 | Levels tested by gavage in New Zealand White strain - 0, 10, 30, and 100 mg/kg. Teratogenic NOEL > 100 mg/kg (HDT). Maternal NOEL > 100 mg/kg (HDT). | | Supplementary<br>004695 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Res. and Consulting Co.; Switz<br>94762; 7/24/87 | Baytan tech. 97% | 403078-05<br>408877-03 | Maternal NOEL = 8 mg/kg. Maternal LEL = 40 mg/kg (decreased body weight gains and food consumption. Developmental NOEL = 40 mg/kg. Developmental LEL = 200 mg/kg (153-175 mg/kg actual conc.). Postimplantation loss, reduced fetal body weight, increased incidence of fetus with skeletal findings. | | Supplementary<br>006809<br>007290 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>86475 & 12390; 1/23/84 | KWG 0519 (Baytan) 97.5%<br>Batch 81606-6128 | 073427 | Levels tested in WISW (SPF-Cpb) strain - 0, 20, 100 and 500 ppm. Maternal NOEL = 100 ppm. Maternal LEL = 500 ppm (body wt. reduction and organ wt. changes) Offspring NOEL = 100 ppm Offspring LEL = 500 ppm (body wt. reduction) Reproduction NOEL > 500 ppm. | | Minimum<br>005337 |

BITERTANOL
(Baycor)

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 087AA- Ä-[(1,1'-Biphenyl)-4-yloxy]-Ä-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol FILE LAST PRINTED: 11/08/91

(Baycor)

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(b)<br>Feeding/oncogenic-2 year<br>Species: mice<br>Bayer AG Institt. Fur Tox. Germ<br>10103; 8/10/81 | Baycor - tech (94 - 95% pure) | 071091 | Oncogenic NOEL > 500 ppm (HDT). Levels tested = 0, 20, 100, 500 ppm in SPF mice. NOEL = 100 ppm. LEL = 500 ppm - reduced body weight. | | Minimum<br>002588 |
| 83-1(a) and 83-2(a)<br>Feeding/oncogenic-2 year<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>10104; 8/10/81 | Baycor (Tech 94% pure) | 071090 | Oncogenic NOEL => 500 ppm (HDT). Systemic NOEL = 100 ppm. Systemic LEL = 500 ppm (decr. body wt. in both sexes, lower kidney wt. (M & F), male adrenals, female liver, higher adrenal & spleen wts (M), Levels tested in SPF str: 0, 20, 100 & 500 ppm. | | Minimum<br>002588 |
| 83-1(b)<br>Feeding-2 year<br>Species: dog<br>Bayer AG Institt. Fur Tox. Germ<br>12307; 12/15/83 | Baycor - tech (97.3%) KWG 0599 Batch #1616001/78 | 073455<br>262114<br>40163-01<br>401864-01 | Beagle dogs (4/sex/dose) given in diet 0, 10, 40, or 160 ppm for 2 years NOEL < 10 ppm (LDT) (body weight decrease at all doses males and females (10 to 20%); vaculolation of epithelial cells of the zona reticularis of adrenal gland in all male and female treatment groups). 3 dogs (160 ppm) had cataracts.<br>Addendum: Issues raised have been resolved; NOEL based on liver, adrenal and eye effects is 10 ppm (0.25 mg/kg); the LEL = 40 ppm (1.0 mg/kg)<br>Classification upgraded to minimum when 20 month dog study is included. | | Suplementary<br>004638<br>005645<br>Min (w 20 mon)<br>006528 |
| 83-1(b)<br>Feeding- 20 month<br>Species: dog<br>Bayer AG Institt. Fur Tox. Germ<br>12328; 12/21/83 | Baycor - tech (96.3 to 96.7%) KWG 0599 | 073455<br>262114<br>4016323<br>401632-01<br>401864-01 | Beagle dogs (6/sex/dose) fed in diet 0, 3, 25 ppm for 12 months; 200ppm for 20 months (Note: control group sacrificed at 12 month, therefore 200 ppm not evaluated past 12 months). NOEL < 3.0 ppm (LDT). Leukocyte values decr 13 to 17 percent for all groups at 12 months; reticulocyte values decreased 22 to 40 percent for 25 and 200 ppm groups. Increased liver enzyme activity at all doses (male and females) at 25 and 51 weeks.<br>Addendum: Issues raised resolved when considered with the 2 year dog study, classification is core minimum. NOEL based on eye effects is 25 ppm (0.63 mg/kg); LEL = 200 ppm (5.0 mg/kg). | | Supplementary<br>004638<br>005645<br>Min w 2yr stud<br>006258 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>53072; 3/12/77 | Baycor Tech. | 099184<br>072868<br>072869<br>246588 | Teratogenic and reproduction effects at 30 and 100 mg/kg/day NOEL = 10 mg/kg/day.<br>IN HOUSE REEVALUATION<br>Teratogenic NOEL = 30 mg/kg. Teratogenic LEL = 100 mg/kg. (malformations i.e. cleft palate, kinked tail, rib dysplasia). Maternal NOEL = 30 mg/kg Maternal LEL = 100 mg/kg.(reduced body weight, diarrhea, unthrifty).<br>Fetotoxic NOEL = 10 mg/kg. Fetotoxic LEL = 30 mg/kg (stunted and slight bone anomalies of the sternum). Levels tested = 0, 10, 30, 100 mg/kg. | | Minimum<br>002117<br>004073<br>Minimum<br>002118 |

# U.S. ENVIRONMENTAL PROTECTION AGENCY
## OFFICE OF PESTICIDES/HED/SACB
## TOX ONELINERS



TOXCHEM NO. 087AA- Ã-[(1,1'-Biphenyl)-4-yloxy]-Á-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>St. Marianna School of Med. Ja<br>7/13/81 | Baycor Tech. (95% purity) | 071090 | Teratogenic NOEL => 65 mg/kg/day (HDT). Maternal NOEL = 10 mg/kg/day Maternal LEL = 25 mg/kg/day (decreased body weight gain). Fetotoxic NOEL = 10 mg/kg/day. Fetotoxic LEL = 25 mg/kg/day (delay ossification of sternebrae & increased incidence of lumber ribs). Dosage Levels = 10, 25, 65 mg/kg. | | Supplementary<br>002588<br>003764 |
| 83-3(a)<br>Developmental- inhalation<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>002; 6/30/81 | Baycor Tech. 93.7% | 071091 | Maternal NOEL = 60 mg/m3. Maternal LEL = 115 mg/m3. Embryotoxic LEL = 27 mg/m3 (increased fetal runts). Terata NOEL > 115 mg/m3 (HDT). Dosage levels = 27, 60, 115 mg/m3 (animals exposed via inhalation for 4 hours/ day from days 6-15 of gestation). | | Supplementary<br>003413<br>002588<br>003764 |
| 83-3(a)<br>Developmental- inhalation<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>011 & 68923; 6/30/81 | Baycor Composite sample<br>unspecified purity | 071091<br>072868<br>072869 | Terata NOEL > 22.38 mg/m3 (HDT). Fetal NOEL > 22.38 mg/m3. Dosage levels = 2.93, 6.35, 22.38 mg/m3 (animals exposed via inhalation for 4 hours/ day from 6-15 of gestation). | | Supplementary<br>003413<br>002588<br>003764<br>004073 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>St. Marianna Univ, Jap<br>7/13/81 | Baycor Tech. | 071090 | Teratogenic NOEL => 65 mg/kg/day (HDT). Maternal NOEL = 10 mg/kg/day. Maternal LEL = 25 mg/kg/day. (Decr. body wt. gain). Fetotoxic NOEL = 10 mg/kg/day. Fetotoxic LEL = 25 mg/kg/day (delayed ossification of sternebrae & incr. incid of lumber ribs). Doses: 10, 25 and 65 mg/kg. | | Supplementary<br>002588<br>003764 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Bayer AG Institt. Fur Tox. Germ<br>10979 & 82239; 6/30/82 | Baycor Tech. 96.7% | 071091<br>072868<br>072869<br>073272 | Maternal NOEL = 30 mg/kg. Maternal LEL = 100 mg/kg (reduced body weight gain, hematuraia). Fetotoxic NOEL= 30 mg/kg. Fetotoxic LEL = 100 mg/kg (increased resorptions, reduced fetal weights). Teratogenic NOEL > 100 mg/kg/day (HDT). Dosage levels = 0, 10, 30, 100 mg/kg/day. | | Minimum<br>004442<br>Supplementary<br>004073<br>003764<br>002588<br>003412 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Bayer AG Institt. Fur Tox. Germ<br>811548; 2/9/83 | Baycor - Tech. 93.9%<br>KMG0599 | 073447 | Himalayan rabbits (15/dose) given by intubation 0, 10, 30, or 100 mg/kg/d on gestation day 6 through 18. Maternal NOEL = 30 mg/kg/day. Maternal LEL = 100 mg/kg/day (lower body weight; lower pregnancy rate; increase number of resorptions). Fetotoxic NOEL = 30 mg/kg/day. Fetotoxic LEL = 100 mg/kg/day (lower mean fetal body weight). Teratogenic NOEL = 30 mg/ kg/day. Terata LEL = 100 mg/kg (1 case club foot; 2 cases cleft palate; 4 cases pigeon chest; 1 case<br>Addendum: Classification unchanged; individual data on visceral and skeletal anomalies and malformations still missing. If these data can not be provided, this study will need to be repeated. | | Supplementary<br>004638<br>005645<br>Supplementary<br>006528 |

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 087AA- Ã-[(1,1'-Biphenyl)-4-yloxy]-Á-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Res. and Consulting Co.; Switz<br>94703; 1/13/87 | Baycor 96.9% | 405146-01 | Range Finding Study. Levels tested in chinchilla str: 0, 10, 50 & 200 mg/kg/day by gavage. Developmental NOEL > 200 mg/kg. | | Supplementary<br>006749 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Mobay Chem.<br>94703; 1/13/87 | Baycor tech. 96.9% | 405146-01 | Dose Range Finding. Maternal NOEL > 200 mg/kg (HDT). Doses: 0, 10, 50 and 200 mg/kg by gavage to Chinchilla rabbits. | | Supplementary<br>006750 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Mobay Chem.<br>94704; 5/8/87 | Baycor Tech 96.9% | 404908-01 | Maternal NOEL = 50 mg/kg. Maternal LEL = 150 mg/kg. Developmental tox Develop. NOEL = 50 mg/kg. Develop. LEL = 150 mg/kg<br>Doses: 0, 10, 50, 150 and 250 mg/kg by gavage to Chinchilla rabbits. | | Supplementary<br>006750<br>Minimum<br>007014 |
| 83-4<br>Reproduction-3 generation<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>10024; 6/30/81 | Baycor Tech. 95% purity | 071091 | Reproduction NOEL = 20 ppm. Reproduction LEL = 100 ppm (reduction of survival of pups from day 5 to weaning). Maternal NOEL = 20 ppm. Maternal LEL = 100 ppm (decreased mean body weights). Dosage levels = 20, 100, 500 ppm. | | Minimum<br>002588 |
| 82-1(a)<br>Feeding-13 week<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>67074; 12/13/78 | Baycor TECH | 009184 | NOEL = 100 ppm. LEL = 300 ppm, (reduced body weight and increase in alkaline phosphatase activity in males). | | Minimum<br>006018<br>001349 |
| 82-1(a)<br>Feeding-13 week<br>Species: rat<br>Res In An. Sci Bioch Tox; Jap.<br>90891; 7/81 | Baycor - Tech. (95% ai) | 261719 | Levels tested = 0, 40, 200, 1000 ppm in Sprague-Dawley strain. NOEL < 40 ppm (LDT) (reduced body wt. gain in males). At 200 & 1000 ppm - both sexes had reduced body weight gain. At 1000 ppm hepatotoxicity - (M/F); bile duct proliferation (F); & changes in esophagus, stomach, & adrenal cortex (M/F). | | Supplementary<br>005568 |
| 82-1(b)<br>Feeding-13 week<br>Species: dog<br>Bayer AG Instit. Fur Tox. Germ<br>8053; 1/12/79 | Baycor (90.2% tech.) | 099184 | NOEL = 1 mg/kg. LEL = 5 mg/kg (local and histological changes on skin).<br>Note: produced keratitis of the cornea at 25 mg/kg. | | Guideline<br>006018 |

UNICONAZOLE

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 207H- Uniconazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(a)<br>Chronic/onco feeding<br>Species: rat<br>Hazleton Lab America<br>HLA 343-191-CIT; 6/2/89 | Uniconazole 97.2% a.i. PKG 84075; Uniconazole 98.3% PYG 85105 | 411620-06 | No increase in neoplastic findings. NOEL = 200 ppm (7.78 mg/kg/day). LEL = 1000 ppm (39.41 mg/kg/day) - reduced body weight gain., increased centrilobular hepatocellular enlargement & vacuolization in M&F; decr. cholesterol in females. Doses tested: 0, 10, 40, 200, & 1000 ppm in Crl:CD(BR)SD str. | | Guideline<br>007994<br>008058 |
| 83-1(b)<br>Feeding-1 year<br>Species: dog<br>Hazleton Lab America<br>HLA 343-202; 12/12/88 | Uniconazole-P 97.4%, lot PYG 86112 | 411620-01 | NOEL = 2 mg/kg/day. LEL = 20 mg/kg/day (increased absolute and relative liver weights in male dogs). Hepatocellular enlargement with increased cytoplasmic homogeneity; increased bile pigments - 200 mg/kg/subject Doses tested: 0, 2, 20, 200 mg/kg/day by capsule to beagle dogs. | | Guideline<br>007994 |
| 83-2(b)<br>Oncogenic<br>Species: mice<br>Hazleton Lab America<br>343-190-CIT; 5/4/89 | Uniconazole-P 98.3% a.i. Lot PYG 85105 | 411620-05 | NOEL = 200 ppm (30 mg/kg/day). LEL = 1500 ppm (225 mg/kg/day). Increased absolute and relative liver weight; hepatocellular enlargement; focal chronic inflammation and necrosis, pigmented macrophages. Incr. incid. of hepatocellular adenomas/carcinomas in males only. Doses tested: 10, 40, 200, 1500 ppm in diet of mice str. Crl:CD-1(ICR)BR. | | Guideline<br>007994 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Sumitomo Chem Co. Japan<br>8603; 2/12/87 | Uniconazole-P 97.2% a.i.; lot PKG 84075 | 404626-09 | Maternal NOEL = 5 mg/kg/day. Maternal LOEL = 25 mg/kg/day. Developmental NOEL = 1 mg/kg/day. Tentative Develop LEL = 5 mg/kg/day. Maternal toxicity based on decreased body weight gain. Developmental toxicity based on extra cervical ribs at 5 mg/kg and and increased incidence of 14th rib at 25 and 50 mg/kg. Tentative based on HED Peer Review committee meeting on 9/7/90. Doses tested: 0, 1, 5, 25 and 50 mg/kg/day in SIC rats. | | Supplementary<br>007994<br>008136<br>008329 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Hazleton<br>343-196; 4/16/87 | Uniconazole-P 98.3% a.i. Lot #PKG 85105 | 404626-10 | Maternal NOEL = 10 mg/kg/day. Toxicity: reduced food consumption & body weight gain during dosing. Developmental NOEL = 20 mg/kg (HDT). Doses tested: 0, 1, 3, 10 and 20 mg/kg in NZW rabbits. The high dose (20 mg/kg/day) used was supported by a range finding study (HLA343-171; 10/23/86) based on HED Developmental Peer Review Committee meeting on 9/7/90. | | Minimum<br>007994<br>008136<br>008329 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Hazleton<br>343-201-CIT; 5/4/89 | Uniconazole 98.3% a.i. Lot # PYG-85105 | 411620-04 | Doses tested in diet of Crl:CD(SD)Br strain: 0, 15, 150 & 1500 ppm (0, 0.75, 7.5 & 75 mg/kg/day). NOEL (parental) = 150 ppm (7.5 mg/kg/day) LOEL (parental) = 1500 ppm (75 mg/kg/day). Toxicity: incr. liver weight, liver hypertrophy and vacuolization. Reprod NOEL = 150 ppm (7.5 mg/kg/day). Reprod LOEL = 1500 ppm (75 mg/kg/d Toxicity: reduced pup weight during lactation. | | Minimum<br>008136 |

TOXCHEM NO. 207N- Uniconazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 85-1<br>Metabolism<br>Species: rat<br>Sumitomo Chem Co. Japan<br>417 & 631; 7/16/87 | C14-triazole labeled Uniconazole | 404967-01 | Rats were dosed with C14-Uniconazole at single oral doses of 1 & 200 mg/kg & at repeated doses of uniconazole at 1 mg/kg, followed by administration of a single oral dose of labeled uniconazole at 1 mg/kg. Uniconazole was rapidly absorbed, extensively metabolized, & rapidly excreted, & there was no indication of bioaccumulation in any tissue or organ. Over a 3 day period, most (96-99%) of the test compound administered was excreted from the animals. The radioactivity recovered in the urine, feces, and CO2 in the exhaled air was 40-66, 33-59 and 0.1% of the dose respectively. Five metabolites (83-91% of the dose) were identified in the urine and feces. The major metabolites of uniconazole were two oxidation products (58-75% of the dose) of the methyl moiety of the tert-butyl group and a free triazole (3-15% of the dose). | | Acceptable<br>008136 |
| 88<br>Peer review - Teratology<br>Species:<br>9/7/90 | Uniconazole | | The Review Committee agreed that uniconazole should be classified as a developmental toxicant - 9/7/90. | | 008329 |

203

PROPICONAZOLE
(Tilt)

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 323EE- 1-[[2-(2,4-Dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole FILE LAST PRINTED: 11/08/91

Propiconazole (Tilt)

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(b)<br>Feeding/oncogenic-2 year<br>Species: mice<br>Huntingdon Res. Centre, Eng.<br>CBG 1968187; 11/4/82 | CGA 64250 Tech. Batch#<br>P 4-6 | 250784-<br>250786<br>251237<br>073919 | Levels tested in Cd-1 strain: 0, 100, 500 & 2500 ppm.<br>Sys NOEL = 100 ppm. Sys LEL = 500 ppm; decr. body wt. gain; incr. liver lesions in males; incr. liver wt. in males; at 2500 ppm - incr. male mortality, incr. liver tumors in both sexes; increased food consumption males; incr. conversion ratios; incr. SGPT and SGOT in both sexes; incr. SAP (M); incr. liver wt. in both sexes; hepatocyte enlargement; vacuolation & fat deposition in liver. Oncogenic NOEL = 500 ppm. Oncogenic LEL = 2500 ppm (incr. incid. of benign and/or malignant male liver tumors. (48/64 at HDT; US 28/64 in control). | | Minimum<br>004287<br>005352 |
| 83-1(a) and 83-2(a)<br>Oncogenic-2 year<br>Species: rat<br>Huntingdon Res. Centre, Eng.<br>789023; CBG1938284; 9/30/82 | CGA 64250 Tech. | 250787-<br>250790<br>073918 | Levels tested: 0, 100, 500, 2500 ppm in SD(CD):crl strain.<br>Oncogenic NOEL > 2500 ppm (HDT); Sys NOEL = 100 ppm. Sys LEL = 500 ppm (hepatocyte changes at 500 ppm (M) and 2500 ppm (both sexes). Exocrine atrophy-pancreas (F) at 500 & 2500 ppm). Luminal dilation - uterus: 2500 ppm. | | Supplementary<br>004295<br>Minimum<br>005352 |
| 83-1(b)<br>Feeding-1 year<br>Species: dog<br>Food & Drug Res Lab, Waverly<br>7737; 5/28/85 | CGA 64250 90.2% a.i.<br>Tech. | 073928 | Dietary: 0, 5, 50, 250 ppm in beagles. NOEL = 50 ppm.<br>LEL = 250 ppm (mild irritation of stomach mucosa). | | Minimum<br>005352 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Ciba-Geigy Corp. Inc.<br>790011; 9/10/79 | CGA 64250 Tech 88% | 244272 | Teratogenic NOEL > 300 mg/kg (HDT). Fetotoxic NOEL = 30 mg/kg.<br>Fetotoxic LEL = 100 mg/kg (ossification retardation).<br>Maternal NOEL = 100 mg/kg. Maternal LEL = 300 mg/kg (decreased body wt. gain & food consumption). Doses: 0, 30, 100 & 300 mg/kg; Tif:Raif (SPF). | | Minimum<br>000789<br>Minimum<br>004316 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Ciba-Geigy Corp. Inc.<br>86004; 1/28/87 | Tilt, Batch FL850083<br>92.1% | 40425001 | Levels tested by gavage on gestation days 6-15 on Crl:COBS BS CD(SD) BR VAS/PLUS: 0, 30, 90 and 360/300 mg/kg/day. Maternal NOEL = 30 mg/kg/day. Maternal LEL = 90 mg/kg/day (reduced body weight gain and occurrence of rales in 1/24 females).<br>Developmental NOEL = 30 mg/kg. Developmental LEL = 90 mg/kg (incr. incidence of unossified sternebrae, rudimentary ribs, and shortened or absent renal papillae. A/D ratio = 90/90 = 1.0. At 360/300 mg/kg (high incidence of rudimentary ribs, unossified sternebrae and shortened or absent renal papillae and altered ureter. | | Minimum<br>006731 |

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 323EE- 1-[[2-(2,4-Dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Ciba-Geigy Corp. Inc.<br>790009; 9/10/79 | CGA 64250 (Tech 88%). | 244272 | Teratogenic NOEL > 180 mg/kg (HDT). Mat NOEL > 180 mg/kg (HDT) Fetotoxic NOEL > 180 mg/kg (HDT). Doses: 0, 30, 90 and 180 mg/kg in Chincilla strain. strain. | | Minimum<br>000789 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Ciba-Geigy Corp. Inc.<br>86043 (MIN.852172); 8/1/86 | CGA 64250 Tech.; purity 92.1% | 265796 | Doses: 0, 100, 250 & 400 mg/kg orally from day 7-19. Maternal NOEL = 100 mg/kg. maternal LEL = 250 mg/kg (decr food consump. and wt. gain seen. Developmental NOEL > 400 mg/kg (HDT). At 400 mg/kg- decr. food consump. & wt. gain; incr resorptions. A/D ratio =< .25 | | 005782<br>Minimum<br>006457 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Ciba-Geigy Corp. Inc.<br>790010; 6/29/81 | CGA 64250 (Tech 91.9%) | 072206 | All F0 females died at 5000 ppm (HDT). No NOEL for toxicity. Reprod. NOEL = 2000 ppm. Levels tested: 0, 400, 2000 & 5000 ppm in Tif:RAIF (SPF) strain. | | Supplementary<br>004276 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Toxigenics (Decatur, Ill.)<br>450-1202; 3/12/85 | CGA 64250 | 073923-<br>073927 | Dietary: 1, 100, 500, 2500 ppm. Parental NOEL = 100 ppm; LEL = 500 ppm incr. incid. of hepatic clear cell change). Reprod NOEL => 2500 ppm (HDT) Develop NOEL = 500 ppm. Develop. LEL = 2500 ppm (decreased offspring survival, body weight depression, increased incidence of hepatic lesions) A/D ratio =< 0.2 (<100/500). At 500 ppm - decr. body wts & incr. incid. of hepatic swelling. | | Minimum<br>005352 |
| 82-1(a)<br>Feeding-3 month<br>Species: rat<br>Ciba-Geigy Corp. Inc.<br>790014; 8/30/79 | CGA 64250 (Tech 88%) | 244272 | NOEL = 240 ppm. LEL = 1200 ppm (reduced body wt. in females). Doses tested: 0, 240, 1200 & 6000 ppm TIF:(RAIF) SPF strain. | | Minimum<br>000789 |
| 82-1(b)<br>Feeding-3 month<br>Species: dog<br>Ciba-Geigy Corp. Inc.<br>8/9/79 | CGA 64250 (Tech 88%) | 244272 | NOEL = 50 ppm. LEL = 250 ppm (lymphoid follicles in the mucous membranes of the pyloric part of the stomach). Doses: 0, 50, 250, 1250 ppm in beagle strain. | | Minimum<br>000789 |
| 82-2<br>Dermal-3 week<br>Species: rabbit<br>Pharmakon Res. Inst. Inc.<br>PH430-CG-00182; 8/30/82 | CGA-64250 Tech. | | Systemic NOEL > 1000 mg/kg/day. No NOEL for skin lesions. Levels tested: 3, 30, 1000 mg/kg/day | | Minimum<br>003994 |

Page_____ is not included in this copy.

Pages 206 through 211 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

✓ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

# U.S. ENVIRONMENTAL PROTECTION AGENCY
# OFFICE OF PESTICIDES/HED/SACB
# TOX ONELINERS



TOXCHEM NO. 480G- Hexaconazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | CORE/GRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(a)<br>Feeding/oncogenic-2 year<br>Species: rat<br>ICI Central Tox. Lab.<br>CTL/P/1920; 8/88 | Hexaconazole, 89.8-90.0% a.i. | 409448-08<br>410847-02 | Doses: 0, 10, 100, 1000 ppm in diet. NOEL = 10 ppm = 0.47 mg/kg/day (M); 0.61 mg/kg/day (F). LEL = 100 ppm = 4.7 mg/kg/day (M); 6.1 mg/kg/d (F). MTD = 1000 ppm = 47 mg/kg/day (M); 61 mg/kg/d (F). Appears to be oncogenic at the high dose, inducing benign Leydig cell tumors (testes). | | Guideline<br>007917 |
| 83-1(b)<br>Feeding-1 year<br>Species: dog<br>ICI Central Tox. Lab.<br>CTL/P/1942; 4/88 | Hexaconazole, 87.9% | 409448-10<br>410847-04 | Doses: 0, 2, 10, 50 mg/kg/day. NOEL = 2 mg/kg/day. LEL = 10 mg/kg/day in male & female beagle dogs, based on increased liver weight and fatty infiltration. | | Supplementary<br>007917 |
| 83-2(b)<br>Oncogenic<br>Species: mice<br>ICI Central Tox. Lab.<br>CTL/P/1929; 12/9/88 | Hexaconazole, 90% a.i. | 409448-09 | Male & female C57Bl/10J:CD-/Alpk mice were dosed with feed containing 5, 40 or 200 ppm hexaconazole (approx. 0.66, 5.3 or 26.3 mg/kg/day). No overt signs or incr. mortality due to treatment were reported. Body weight gains were significantly decreased in males at 200 ppm. Males & females had centrilobular fatty change and hepatic hypertrophy due to the high dose. Males were affected more than females. hexaconazole is not an oncogen in male or female mice. LEL = 200 ppm (M&F) mice. NOEL = 40 ppm in male and female mice. | | Minimum<br>007917 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>ICI Central Tox. Lab.<br>CTL/P/1127 &/1127S; 12/84 | Hexaconazole, 92.3% a.i. | 409448-11 | Doses: 0, 2.5, 25, 250 mg/kg/day in Alpk:AP strain.<br>Maternal NOEL = 25 mg/kg/day. Maternal LEL = 250 mg/kg/day based on reduced body weight gain and food consumption.<br>Developmental NOEL = not determined. Developmental LEL = 2.5 mg/kg based on delayed skeletal ossification and extra 14th ribs. At higher doses abnormalities of the urogenital system.<br>Study may be upgraded with adequate historical control data for skeletal abnormalities. Historical control data provided. | | Supplemental<br>007917<br>Guideline<br>008367 |
| 83-3(b)<br>Developmental-rangefinding<br>Species: rabbit<br>ICI Central Tox. Lab.<br>CTL/P/2230; 2/3/89 | Hexaconazole, 90.6% | 410847-05 | LEL = 50 mg/kg/day based upon reduced food consumption and one death (females only). Used to establish dosing for an embryotoxicity study. Doses tested: 0, 25, 50 & 100 mg/kg/day. | | Supplementary<br>007917 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>ICI Central Tox. Lab.<br>CTL/P/2239 &/2239S; 11/28/88 | hexaconazole, 93.0% a.i. | 410487-06<br>413847-02 | Doses: 0, 25, 50, 100 mg/kg/day. Maternal NOEL NZW rabbits = 50 mg/kg/day LEL = 100 mg/kg/day based on decr. gestational body weight gain.<br>Developmental NOEL = 25 mg/kg/day, LEL = 50 mg/kg/day based on early intrauterine death. | | Supplementary<br>007917 |

212

TOXCHEM NO. 480G- Hexaconazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>ICI Central Tox. Lab.<br>CTL/T/2678; 1/12/90 | Hexaconazole 88.1% a.i. | 413847-01 | Doses: 0, 200, 300, 400 mg/kg/day. NOELs not determined. Maternal and Developmental LELs = 200 mg/kg/day based on mortality and fetotoxicity, respectively. All mid and high dose rabbits died. Only one low dose litter was produced. Only 4/9 controls were pregnant at termination. | | Invalid<br>007917 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>ICI Central Tox. Lab.<br>CTL/P/1131 &/1131S; 11/84 | Hexaconazole, 92.3% a.i. | 409448-12 | Doses: 0, 2.5, 12.5, 50.0 mg/kg/day. No treatment related effect reported | | Supplementary<br>007917 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>ICI Central Tox. Lab.<br>CTL/P/1598; 4/88 | Hexaconazole, 90.0% a.i. | 409448-13 | Doses: 0, 20, 100, 1000 ppm in diet of Alpk:APfSD Wistar derived strain. Reproductive NOEL = 100 ppm. reprod. LEL = 1000 ppm based on decr. body weight gain and pup survival.<br>Systemic NOEL = 20 ppm. Systemic LEL = 100 ppm based on liver pathology. | | Guideline<br>007917 |
| 82-1(a)<br>Feeding-3 month<br>Species: rat<br>ICI Central Tox. Lab.<br>CTL/P/1073 &/1073S; 11/29/84 | Hexaconazole, 92.8% | 409448-05 | Doses: 0, 50, 500, 5000 ppm in diet of Alpk/AP (Wistar derived str M & F) NOEL = 50 ppm (2.5 mg/kg/day). LEL = 500 ppm (25 mg/kg/day). MTD=100 ppm (50 mg/kg/day), based on fatty change & hypertrophy of the liver. | | Supplementary<br>007917 |
| 82-1(b)<br>Feeding-3 month<br>Species: dog<br>ICI Central Tox. Lab.<br>CTL/P/1137 &/1137S; 11/84 | Hexaconazole, 92.7% | 409448-06 | Doses: 0, 5, 25, 125 (75/150) mg/kg/day. NOEL in male & female = 5 mg/kg LEL = 25 mg/kg/day based on elevation of SGPT and AP and decreased triglycerides and cholesterol, and fatty liver. | | Minimum<br>007917 |
| 82-2<br>Dermal-3 week<br>Species: rat<br>ICI Central Tox. Lab.<br>CTL/P/1944; 10/87 | Hexaconazole, 87.9% | 409448-07 | Doses: 0, 100, 300, 1000 mg/kg/day. NOEL (M&F) > 1000 mg/kg/day in Alpk:AP strain | | Guideline<br>007917 |
| Feeding-28 day<br>Species: mice<br>ICI Central Tox. Lab.<br>CTL/P/2204; 2/3/89 | Hexaconazole, 92.3% | 411428-01 | Doses: 0, 25, 100, 500, 1500 ppm in diet. NOEL in C5788/10JfCD-1/Alpk male & female mice was 25 ppm based on hepatotoxicity and reduced body wt gains. LEL was 100 ppm. | | Supplementary<br>007917 |

TOXCHEM NO. 272E- Cyproconazole FILE LAST PRINTED: 11/08/91

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Res. and Consulting Co.; Switz<br>048701; 7/9/85 | Cyproconazole tech 95.6%<br>pure Batch# 8507 | | Range Finding Study - Levels tested to Wistar KFK-HAN strain by gavage on 6 - 15 day of gestation: 0, 7.5, 30, 75, and 120 mg/kg. Maternal NOEL < 7.5 mg/kg (decrease food consumption) at 30 mg/kg - inhibited body weight gain. Developmental NOEL = 7.5 mg/kg , Developmental LEL = 30 mg/kg ( increased early resorption, post implantation, decrease fetal body weight, and increase cleft palate) | | Supplementary<br>007003 |
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Res. and Consulting Co.; Switz<br>053886; 3/21/86 | SAN 619F tech 95.6% | 406077-20 | Maternal NOEL = 10 mg/kg , Maternal LEL = 50 mg/kg (inhibited body weight gain during treatment & decrease food consumption [equivocal] ). Developmental NOEL < 2 mg/kg. Embryo/fetal toxicity at 10 mg/kg (mid-dose): increased inc. of embryonic & fet. resorptions. Teratogenicity (positive): hydrocephalus internus at all dose levels (2, 10, & 50 mg/kg), agenesis of the left kidney & ureter (50 mg/kg). | | Supplementary<br>007003 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Sandoz Ltd<br>6712; 7/8/87 | Cyproconazole tech 95.6%<br>Lot# 8507 | 406077-23<br>412945-00 | Levels tested in KFM Wistar strain - 0, 4, 20, & 120 ppm (0.4, 1.7, & 10.6 mg/kg). NOEL = 0.4 mg/kg , LEL = 1.7 mg/kg. Parameters affected at 1.7 mg/kg (mid-dose): increase duration of gestation (Fo only) & decrease litter sizes (F1 & F2). Test compound stability data and sampling techniques for dietary analyses are satisfactory (5/3/90). | | Minimum<br>007003<br>007908 |
| 82-1(a)<br>Feeding-13 week<br>Species: rat<br>Sandoz Ltd<br>353/354/R; 4/86 | Cyproconazole tech 95.7% | 406077-18 | Levels tested in Han Wistar strain - 0, 20,80, and 320 ppm (1,4,& 16 mg/kg). NOEL < 1 mg/kg. Changes at 16 mg/kg (HDT): inhibited B.W. gain, increased creatinine, increased sodium, and decreased calcium. Increased creatinine also seen at 1mg/kg(LDT) but not at 4 mg/kg (mid-dose). NOEL = 20 ppm. | | Minimum<br>007003<br>007907 |
| 82-1(b)<br>Feeding-13 week<br>Species: dog<br>Res. and Consulting Co.; Switz<br>6521/86 | Cyproconazole tech 95.6% | 406077-19 | Levels tested in beagles - 0, 20, 100, & 500 ppm(0, 0.8, 4.0, & 20 mg/kg). NOEL = 0.8 mg/kg , LEL = 4 mg/kg (increased ab. liver weight & hepatocytomegaly) | | Supplementary<br>007003 |
| 82-2<br>Dermal-3 week<br>Species: rabbit<br>Sandoz Ltd<br>LMP415-RB; 4/20/88 | Cyproconazole tech 95.6% | 406243-04 | Levels tested in NZW strain - 50, 250 and 1250 mg/kg. NOEL = 250 mg/kg; LEL = 1250 mg/kg (inhibited B.W. gain/food consumption (M), increased AST, increased creatinine, increased cholesterol) | | Minimum<br>007003 |
| 82-2<br>Dermal-3 week<br>Species: rabbit | Cyproconazole WG-40 Formulation | | Data requirement waived-based on other sufficient dermal toxicity data | | 007282 |

Appendix 11. 1- Liners for Tebuconazole

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-1(a) and 83-2(a) Feeding/oncogenic-2 year Species: rat Bayer AG Instit. Fur Tox. Germ 16375; 1/25/89 | HWG 1608 (Terbuconazole 95% a.i.) | 407009-39 408164-01 | Sytemic NOEL = 100 ppm. Systemic LEL = 300 ppm (based on body wt. depression; decr. hemoglobin, hematocrit, MCV and MCHC; incr. liver enzymes). Not oncogenic at the dose level tested. Levels tested: 100, 300 & 1000 ppm (5.3, 15.9 & 55 mg/kg/bw, males; 7.4, 22.8 & 86.3 mg/kg/bw in females). | | Minimum 007200 |
| 83-1(a) and 83-2(b) Oncogenic Species: mice Bayer AG Instit. Fur Tox. Germ 16376A; 12/12/91 | HWG 1608 (Tebuconazole tech.), batch 816896061 96.2% pure | 421750-01 | HWG 1608 was administered to Bor:NMRI(SPF-Han) mice of both sexes for a period of up to 91 weeks in the diet at levels of: 0, 500 and 1500 ppm resulting in mean respective compound intakes of: 0, 84.9 & 279 mg/kg body wt. (M) & 0, 103.1 & 365.5 mg/kg (F). Statistically significantly decr. body weights & increased food consumption were reported that were consistent with decr. food efficiency at 500 & 1500 ppm in males & at 1500 ppm in females. Clinical chemistry values dose-dependent increases in plasma GOT, GPT and AP) for both sexes were consistent with hepatoxic effects at both 500 ppm & 1500 ppm. Relative liver weight increases reached statistical significance at both 500 & 1500 ppm in males & at 1500 ppm only in females. Histopathology included dose-dependent increase in hepatic panacinar fine fatty vacuolation, statistically significant at 500 & 1500 ppm in males and at 1500 ppm in females. Other histopathology included significant oval cell proliferation in both sexes at 1500 ppm and dose-dependent ovarian atrophy that was stat. significant at 500 & 1500 ppm. MTD was achieved at or around 500 ppm. Neoplastic histopathology consisted of statistically incidences of hepatocellular neoplasms: adenomas (35.4%) and carcinomas (20.8%) at 1500 ppm in males and carcinomas only (26.1%) at 1500 ppm in females. In addition, there was a dose-related, but not statistically significant, increase in histiocytic sarcomas in both sexes. In males the incidence amounted to 2.1%, 4.2% and 6.3% at 0, 500 & 1500 ppm, respectively. In females the incidence amounted to 2.1%, 6.7%, and 10.9% respectively. The significance of these histiocytic sarcomas will be assessed pending submission of pertinent historical data. | | Supplementary 009307 |
| 83-1(b) Feeding-1 year Species: dog Bayer AG Instit. Fur Tox. Germ T6018115; 11/11/87 | HWG 1608 (Terbuconazole) 96.9% a.i. | 407009-40 | NOEL = 40 ppm LEL = 200 ppm (based on ocular lesions - lenticular and and corneal opacity and hepatic toxicity - lobulation/swelling, increased iron containing pigments and lipids). Doses tested in beagles: 0, 40 200 and 1000/2000 ppm. | | Minimum 007200 |

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-2(b)<br>Oncogenicity- 21 months<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>16376; 1/25/88 | HWG 1608 (Terbuconazole)<br>95% a.i. | 407009-41 | Dietary levels tested in NMRI mice: 0, 20, 60 and 180 ppm. The HDT resulted in slight liver toxicity (increased bilirubin and weight, associated with centrilobular and periportal vacuolation and lipid deposition); increased adrenal cortical size and hyperplasia and increased pancreatic interstitial edema. Terbuconazole was not oncogenic in mice at the dose levels tested. The MTD was not achieved. Dose in mg/kg: (M: 5.9, 18.2 & 53.1 mg/kg/d; F: 9.0, 26.1 & 80.5 mg/kg/d). | | Supplementary<br>007200 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Res. and Consulting Co.; Switz<br>R4322; 6/1/87 | HWG 1608 (98.2% a.i.)<br>(Terbuconazole) | 407009-42 | Range Finding. Dose levels tested in Wistar rats: 0, 10, 30 & 90 mg/kg/d Minimally toxic at the HDT (slight depression of maternal body weight gain). Doses selected for main teratology study: 0, 30, 60 and 120 mg/kg/day. | | Supplementary<br>007200 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: rat<br>Res. and Consulting Co.; Switz<br>074057; 4/28/88 | HWG 1608 (Terbuconazole<br>98.3% a.i.) | 407009-43 | Maternal NOEL = 30 mg/kg/day. Maternal LEL = 60 mg/kg/day (based on elevation of absolute and relative liver weights).<br>Developmental NOEL = 30 mg/kg/day. Developmental LEL = 60 mg/kg/day (based on delayed ossification of thoracic, cervical and sacral vertebrae sternum, fore and hind limbs and increase in supernumerary ribs).<br>Doses tested (by gavage) in Wistar str: 0, 30, 60 and 120 mg/kg/day. | | Minimum<br>007200 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>16511; 3/8/88 | HWG 1608 (Terbuconazole<br>97.4% a.i.) | 408215-01 | Dose levels tested in NMRI mice: 0, 10, 20, 30 and 100 mg/kg/day. Maternal NOEL = 10 mg/kg/day. Maternal = 20 mg/kg/day (based on reductions of hematocrit). | | Acceptable<br>007200 |
| 83-3(a)<br>Developmental Toxicity Study<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>16527; T5021859; 3/14/89 | HWG 1608 (Terbuconazole<br>93.6% a.i.) | 408215-00 | Maternal NOEL = 10 mg/kg/day. Maternal LEL = 20 mg/kg/day (based on toxicity observed in the "Maternal Toxicity" study).<br>Developmental NOEL = 10 mg/kg/day Developmental LEL = 30 mg/kg/day (based on increased number of runts). Doses tested in NMRI mice: 0, 10, 30 and 100 mg/kg/day. | | Minimum<br>007200 |
| 83-3(b)<br>Developmental-rangefinding<br>Species: rabbit<br>Res. and Consulting Co.; Switz<br>R4321; 2/4/87 | HWG 1608 (terbuconazole)<br>98.2% | 407009-44 | Dose levels tested in Chinchilla rabbits: 0, 30, 100 and 300 mg/kg/day. Maternal NOEL = 100 mg/kg/day. Maternal LEL = 300 mg/kg/day (based on reduced body weight gain and preimplantation losses).<br>Doses selected for main teratology study: 0, 10, 30 & 100 mg/kg/day | | Supplementary<br>007200 |

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 83-3(b)<br>Developmental Toxicity Study<br>Species: rabbit<br>Res. and Consulting Co.; Switz<br>074070; 2/26/87 | HWG 1608 (Terbuconazole 98.2%) | 407009-45 | Maternal NOEL = 30 mg/kg/day. Maternal LEL = 100 mg/kg/day (based on depression of body weight gains and food consumption).<br>Developmental NOEL = 30 mg/kg/day. Developmental LEL = 100 mg/kg/day (based on increased postimplantation losses - early and late resorptions)<br>Doses tested in Chincilla rabbits: 0, 10, 30 & 100 mg/kg/day by gavage. | | Minimum<br>007200 |
| 83-4<br>Reproduction-2 generation<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>16223 & T5017647; 11/12/87 | HWG 1608 (Terbuconazole 95.2% a.i.) | 407009-46 | Maternal NOEL = 300 ppm. Maternal LEL = 1000 ppm (based on depressed body weights, increased spleen hemosiderosis and decreased liver and kidney weights). Reproductive NOEL = 300 ppm. Reprod. LEL = 1000 ppm (based on neonatal birth weight depression).<br>Doses tested in Wistar str: 0, 100, 300 and 1000 ppm. | | Minimum<br>007200 |
| 82-1(a)<br>Feeding-3 month<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>94212; 10/27/86 | HWG 1608 (terbuconazole) 93.4% | 407009-30 | Male NOEL = 400 ppm. LEL = 1600 ppm (based on decreased body wt. gains).<br>Dose levels tested in Wistar rats: 0, 100, 400 & 1600 ppm.<br>Female NOEL: = 100 ppm. LEL = 400 ppm [M: 8.6, 34.8 & 171.7 mg/kg/day; F: 10.8, 46.5 and 235.2 mg/kg/day] | | Minimum<br>007200 |
| 82-1(b)<br>Feeding-3 month<br>Species: dog<br>Bayer AG Institt. Fur Tox. Germ<br>T6016919; 5/6/87 | HWG 1608 (Terbuconazole) 93.4% a.i. | 407009-34 | NOEL = 200 ppm LEL = 1000 ppm (based on decr. body wt. gains; decr. food consumption, incr. N-demethylase activity.<br>Dose levels tested in beagle dogs: 0, 200, 1000 and 5000 ppm.<br>[Males: 73.7, 368.3 & 1749.1 mg/kg/day; Females: 73.4, 351.8 & 1724.8 mg/kg/day]. | | Minimum<br>007200 |
| 82-2<br>Dermal-3 week<br>Species: rabbit<br>Bayer AG Institt. Fur Tox. Germ<br>93093; 5/8/84 | HWG 1608 (Terbuconazole 97.1% a.i.) | 407009-37 | Dose levels tested in N.Z. rabbits: 0, 50, 250 and 1000 mg/kg/day. No significant systemic effects were seen. NOEL > 1000 mg/kg/day. | | Guideline<br>007200 |
| Feeding-28 day<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>T0015905; 11/12/84 | HWG 1608 (Terbuconazole 97% a.i.) | 407009-32 | NOEL = 30 mg/kg/day. LEL = 100 mg/kg/day (based on changes in hematology and clinical chemistry). Wistar rats were treated for 28 days followed by 28 days of recovery. Doses: 0, 30, 100 & 300 mg/kg/day. | | Supplementary<br>007200 |
| Inhalation- 15 days<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>94559; 2/22/85 | HWG 1608 (Terbuconazole 96.2%) | 407009-38 | NOEL = 10.6 mg/m3. LEL = 155.8 mg/m3 (based on piloerection and induction of liver enzymes). Dose levels tested in Wistar rats: 0, 1.2, 10.6 and 155.8 mg/m3 (15 days, 6 hrs/day). | | Minimum<br>007200 |

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| Feeding-30 day<br>Species: dog<br>Bayer AG Instit. Fur Tox. Germ<br>94573; 7/1/86 | HWG 1608 (Terbuconazole)<br>93.4% a.i. | 407009-35 | Range Finding Study: NOEL = 500 ppm. LEL = 5000 ppm (based on elevated alkaline phosphatase). Dose levels tested in beagle dogs for 30 days: 0, 500, and 5000 ppm. | | Supplementary<br>007200 |
| Feeding-8 week<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>T0018885 &T6018539; 7/7/86 | HWG 1608 (terbuconazole<br>96.9%) | 407009-33 | Range Finding Study: Dietary levels tested in SPF inbred mice: 0, 500 and 2000 ppm, 8 week study and 0, 125, 500 and 2000 ppm, 5 day study (enzyme induction). Systemic toxicity (8 week study) consisted of increased absolute and relative liver weight associated with liver necrosis vacuolization degeneration and lipidosis, in both dose levels tested. Microsomal enzymes (5-day study) were induced at all dose levels tested. Dose levels selected for the main mouse oncogenicity study; 0, 20, 60 and 180 ppm. | | Supplementary<br>007200 |
| 84-2(a)<br>Mutagenic-Ames<br>Species: salmonella<br>Bayer AG Instit. Fur Tox. Germ<br>16383 & 216383A; 1/27/88 | HWG 1608 (Terbuconazole<br>96.6% a.i.) | 407009-47<br>407009-48 | Not mutagenic with or without metabolic activation at dose levels ranging from 37.5 to 2400 ug/plate. | | Acceptable<br>007200 |
| 84-4<br>Mutagenic-(HGPRT)<br>Species: CHO cells<br>Bayer AG Instit. Fur Tox. Germ<br>16749; 5/31/88 | HWG 1608 (Terbuconazole<br>96.6% a.i.) | 407009-49 | Not mutagenic in CHO cells with/without metabolic activation at dose levels ranging from 12.5 to 200 ug/plate (no cytotoxicity). | | Unacceptable<br>007200 |
| 84-4<br>Mutagenic-dominant lethal test<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>94404; 8/20/86 | HWG 1608 (Terbuconazole<br>93.5% a.i.) | 407009-50 | Negative for dominant lethal mutations at a dose level of 2000 mg/kg (Only a single dose tested; no positive control). | | Unacceptable<br>007200 |
| 84-4<br>Mutagenic-micronucleus assay<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>13159; 1/4/85 | HWG 1608 (Terbuconazole<br>95.3% a.i.) | 407009-51 | Not genotoxic at dose levels of 200, 500, or 2000 mg/kg. | | Acceptable<br>007200 |
| 84-2(b)<br>Mut-Sister chromatid exchange<br>Species: CHO cells<br>Microbiological Associates<br>T5390.334; 9/3/87 | HWG 1608 (Terbuconazole<br>96.5% a.i.) | 407009-52 | Negative at dose levels of 4 to 30 ug/ml without activation or 15 to 120 ug/ml with activation. | | Acceptable<br>007200 |

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 84-2(b)<br>Mutagenic- in vitro cytogen.<br>Species: human lymphocytes<br>Bayer AG Instit. Fur Tox. Germ<br>16395; 2/2/88 | HWG 1608 (Terbuconazole 96.5% a.i.) | 407009-53 | Negative with/without metabolic activation at dose levels of 30 to 300 ug/ml. (No cytotoxicity was seen without activation). | | Unacceptable<br>007200 |
| 84-2(b)<br>Mutagenic-DNA damage/repair<br>Species: E. coli<br>Bayer AG Instit. Fur Tox. Germ<br>94556; 7/1/83 | HWG 1608 (Terbuconazole 97.1% a.i.) | 407009-55 | Negative with/without metabolic activation at dose levels of 625 - 1000 ug/plate. (No growth inhibition zone was demonstrated in either strain). | | Unacceptable<br>007200 |
| 84-4<br>Mutagenic-unscheduled DNA synt<br>Species: rat prim. hepatocyte<br>Hazleton<br>T5024090; 8/20/88 | HWG 1608 (Terbuconazole 96.5% a.i.) | 408164-02 | Negative for UDS in rat hepatocytes at dose levels ranging from 0.504 to 25.2 ug/ml. | | Acceptable<br>007200 |
| Chemical analysis<br>Species:<br>Mobay Corp., Stilwell, KS<br>96758; 6/16/88 | Folicur (Terbuconazole) 1.2 EC (15.4% a.i.) | 407009-23 | A gas chromatographic method was described for analysis of Folicur in inhalation chamber atmospheres. | | Acceptable<br>007200 |
| 85-1<br>Metabolism<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>M181089-7&181088-6; 12/21/87 | HWG 1608 (terbuconazole); [phenyl-UL-C14]>99%; [Triazole-3,5-C14), 98.4% non radio HWG 1608 99.5% | 409959-11<br>409959-12 | 98.1% of oral dose is absorbed. Over 87% of dose excreted in urine & feces within 72 hrs after dosing. At sacrifice (72 hrs postdosing) total residue (minus GI tract) amounted to 0.63% of the dose. A total of 10 compounds were identified in excreta. A large fraction of the identified metabolites corresponded to successive oxidation steps of a methyl group of HWG 1608. At higher dose (20 mg/kg) changes in detoxification patterns may be occurring. | | Supplementary<br>008241 |
| 85-2<br>Metabolism - dermal absorption<br>Species: rat<br>Mobay Corp., Stilwell, KS<br>87-721-01; 7/28/88 | [Triazole-3,5-C14] HWG 1608, 99.66% radiochem. purity; Non-radioactive HWG 1608 94.7% purity | 409959-13 | In rats dosed dermally at actual doses of 0.604, 5.85, 52.4, & 547 ug/cm2 the percent of the dose absorbed by 24 hrs amounted to 27.77, 27.06,23.01 and 6.38% of the applied dose, respectively. The amount which remained on the application site after soap & water wash increased with dose. | | Acceptable<br>008241 |
| 81-1<br>Acute oral LD50<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>T3015926 &T4015927; 10/13/83 | HWG 1608 (97.1% a.i.) (Terbuconazole) | 407009-17 | LD50 (fasted M) > 5000 mg/kg. LD50 (fasted F) = 3933 (3316.1-566.2) mg/kg LD50 = 4264 mg/kg (3952.3-5330.2) (unfasted M). LD50 (unfasted F) = 3352 mg/kg (2341.4-3977.5) | 3 | Minimum<br>007200 |

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 81-1<br>Acute oral LD50<br>Species: mice<br>Bayer AG Instit. Fur Tox. Germ<br>T5015928; 10/13/83 | HWG 1608 97.1% a.i. (Terbuconazole) | 407009-17 | LD50 (M) = 1615 mg/kg (1057.2-2179.6)<br>LD50 (F) = 3023 mg/kg (2127.4-5072.7) | 3 | Minimum<br>007200 |
| 81-1<br>Acute oral LD50<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>T8015813; 10/13/83 | HWG 1608 97.1% a.i. (Terbuconazole) | 407009-17 | LD50 > 1000 mg/kg (M&F). | | Supplementary<br>007200 |
| 81-2<br>Acute Dermal LD50<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>T3015809; 10/13/83 | HWG 1608 97.1% a.i. (Terbuconazole) | 407009-17<br>412908-01 | LD50 > 5000 mg/kg. No signs of toxicity reported at the dose level tested | 3 | Supplementary<br>007200<br>Guideline<br>007884 |
| 81-3<br>Acute inhalation LC50<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>T2015844 &T3015845; 6/26/87 | HWG 1608 97.1% a.i. (Terbuconazole) | 407009-17 | LD50 > 816 mg/m3 (4 hr. exp). LD50 > 240 mg/m3 (5 daily 8 hr. esposures) | | Supplementary<br>007200 |
| 81-3<br>Acute inhalation LC50<br>Species: rat<br>Bayer AG Instit. Fur Tox. Germ<br>T8025641 &T9025462; 1/17/88 | HWG 1608 (Terbuconazole) 96.2% a.i/ | 407009-22 | LC50 > 371 mg/m3 (aerosol). LC50 > 5093 mg/m3 (dust) | 2 | Guideline<br>007200 |
| 81-4<br>Primary eye irritation<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>T5015847; 10/13/83 | HWG 1608 (Terbuconazole) 97.1% | 407009-17 | Slightly irritating. | 3 | Minimum<br>007200 |
| 81-5<br>Primary dermal irritation<br>Species: rabbit<br>Bayer AG Instit. Fur Tox. Germ<br>5015847; 10/13/83 | HWG 1608 (Terbuconazole) 97.1% | 407009-17 | Nonirritant. | 4 | Minimum<br>007200 |

223

TOXCHEM NO. 128997- Folicur FILE LAST PRINTED: 04/27/92

| CITATION | MATERIAL | ACCESSION/ MRID NO. | RESULTS | TOX CAT | COREGRADE/ DOCUMENT# |
|---|---|---|---|---|---|
| 81-5<br>Primary dermal irritation<br>Species: rabbit<br>Mobay Corp., Stilwell, KS<br>88-323-AV; 10/4/88 | Folicur (Tebuconazole); Tech grade, 96.6% a.i. | 409959-10 | Nonirritant. | 4 | Minimum<br>008241 |
| 81-6<br>Dermal sensitization<br>Species: guinea pig<br>Bayer AG Institt. Fur Tox. Germ<br>T2025339; 11/19/87 | HWG 1608 (Terbuconazole) 97.4% | 407009-28<br>412908-02 | No evidence of skin sensitization when tested by the Buehler Patch test method. | | Supplementary<br>007200<br>Minimum<br>007884 |
| Acute intraperitoneal LD50<br>Species: rat<br>Bayer AG Institt. Fur Tox. Germ<br>T2015808; 10/13/83 | HWG 1608 (terbuconazole) 97.1% | 407009-17 | LD50 (M) = 751 mg/kg (670.9-826.8). LD50 (F) = 395 (329.9-430) mg/kg. | | Guideline<br>007200 |

224