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MEMORANDUM

SEP 14 1992

SUBJECT: Developmental and Reproductive Toxicity Peer Review Of Tebuconazole

FROM: Gary J. Burin, Ph.D., D.A.B.T. 7/27/92
Manager
Developmental/Reproductive Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Alberto Protzel, Ph.D. 8/5/92
Review Section III
Toxicology Branch II

TO: Ms. Susan Lewis
Product Manager, Team 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division Peer Review Committee (PRC) for Developmental and Reproductive Toxicity met on June 3, 1992 to discuss and evaluate the weight-of-the-evidence on tebuconazole with particular reference to its potential for reproductive and developmental toxicity. This was the first evaluation of tebuconazole by the PRC.

The Committee concluded that developmental toxicity was induced in mice, rats and rabbits via the oral route of administration. The lowest NOEL (10 mg/kg/day) is observed in mice. Equivocal maternal toxicity was observed at an oral dose level of 100 mg/kg in the mouse and at 30 mg/kg in the rat. Developmental toxicity was not induced in the rat or mouse at the highest dose tested via the dermal route (1000 mg/kg/day). Additional pharmacokinetics information is suggested to verify that the test conducted in the rat via the dermal route was adequately designed. It was recommended that the NOEL for developmental toxicity (10 mg/kg/day) in the oral mouse developmental toxicity study be used for the assessment of acute dietary risk. The developmental toxicity risk associated with occupational exposure should be assessed based upon the NOEL of 1000 mg/kg/day in the dermal developmental toxicity study conducted in the mouse.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Karl Baetcke

for Marcia Van Gemert

William L. Burnam

Gary J. Burin

Laurence D. Chitlik

James Rowe

Hugh Pettigrew

Stephen Dapson

Reto Engler

Thomas F.X. Collins (FDA)

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Alberto Protzel

3. Peer Review Members in Absentia: (Committee Members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope A. Fenner-Crisp

Jennifer Seed (OPPTS)

Bob Sonawane (ORD)

Jennifer Orme-Zavaleta(OW)

Roger Gardner 8/24/92

David Anderson 8/25/92

B. Material Reviewed:

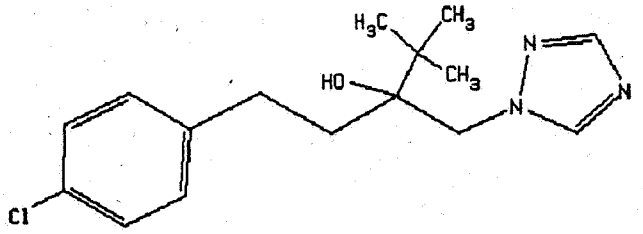
The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Alberto Protzel. The material reviewed is attached to the file copy of this report.

C. Background Information:

This is the first review of tebuconazole by the PRC.

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:



D. ASSESSMENT OF RELEVANT DATA

1. Mice (Oral Dosing)

Study of Embryotoxic Effects on Mice After Oral Administration. March 14, 1988. BAYER AG. MRID 408215-01. This study was accompanied by: Supplementary Study of Maternal Toxicity to Mice After Oral Administration. March 9, 1988. BAYER AG, MRID 408215-01.

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~~

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for visceral malformation by the modified Wilson technique, and approximately 70% were stained for evaluation of skeletal malformations by the Dawson method.

No compound-related mortality, clinical signs or effects on body weight gains were reported during the dosing period or during the entire gestation period. An additional study was conducted to examine further the maternal toxicity of the compound at the dose levels utilized in the aforementioned study. 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, or 100 mg/kg/day. Statistically significant decreases in hematocrit (at 30-100 mg/kg) and mean corpuscular volume (at 20-100 mg/kg) and increased hepatic triglycerides, pale lobular liver and increased severity of hepatic vacuoles and lipidosis were found at 100 mg/kg.

There was a dose-dependent and statistically significant increase in the number of runts per litter (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. There was a statistically significant increase in the number of malformed fetuses per litter (0.65 at the HDT vs 0.04 in controls). There were increases in the number of fetuses and litters with malformations at the high dose level. The malformations were primarily in the skull, brain and spinal column. 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 the frequency of runts at 30 mg/kg (MDT) and 100 mg/kg (HDT). Equivocal maternal toxicity was observed at 100 mg/kg/day.

2. Mice (Dermal Dosing)

References: Embryotoxicity study (including teratogenicity) with HWG 1608 Technical in the mouse (Dermal application). July 16, 1990. BAYER AG. MRID 420103-01. This study was accompanied by: Supplementary study to Embryotoxicity study (including teratogenicity) with HWG 1608 Technical in the mouse (Dermal application). BAYER AG. MRID 408215-01

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 surface 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 technique, and the rest were cleared in potassium hydroxide and stained with alizarin S for evaluation of skeletal malformations.

No compound-related mortality, clinical signs or effects on body weight gains were reported during the dosing period or during the entire gestation period. An additional study was conducted to assess further 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), or 1000 (HDT) mg/kg/day, following the same protocol as the main study. This supplementary study revealed 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. 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 the HDT. Dose-dependent increases were observed in the activities of AST (GOT) and ALT (GPT) in plasma (up to 37% at the HDT).

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

Skeletal findings revealed statistically significant increases in the fetal incidences of several variations. These include: bipartite sternebra 5: fetuses: 11.0% (HDT) vs 3.8% (controls) [($p \leq 0.05$)] and litters: 40% (HDT) vs 20% (controls); supernumerary ribs, one, right: fetuses: 72% (HDT) vs 48% (controls) [($p \leq 0.01$)] and litters 100 % (HDT) vs 88% (controls); 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); right forelimb, non-ossified distal phalanx, digit 4: fetuses: 13% (HDT) vs 9.7% (controls) and litters: 40% (HDT) vs 28% (controls). However, historical control data were not available for these variations and the PRC could not conclude that the increases were compound-related.

The NOEL for developmental toxicity in mice after dermal dosing is equal to 1000 mg/kg/day. Equivocal maternal toxicity was observed at 1000 mg/kg/day. The PRC noted that dams could have tolerated higher dose levels of test compound.

3. Rats (Oral) Range Finding Study -

Reference: Dose range-finding embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rat. June 1, 1987. BAYER AG. MRID 407009-42.

Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant

Wistar/HAN rats (5/dose level) on days 6-15 of gestation at levels of 0, 10, 30, or 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. 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. Mean food consumption was -3.7% of controls at the HDT during treatment. 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).

4. Rat (Oral) Main Study

Reference: Embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rat. April 28, 1988. BAYER AG. MRID 407009-43.

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 technique, and the rest were cleared in potassium hydroxide and stained with alizarin S for evaluation of skeletal malformations.

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 was significantly decreased with respect to controls at the MDT (-7%) and 0 at the HDT (-15%). There was a slight increase in daily food consumption (about 5%) during the post-dosing period. A significant decrease in absolute body weight was reported for the HDT and a dose-dependent and statistically significant increase in liver weight/body weight was reported at the MDT and the HDT. 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.

An increase in the numbers of early and late resorptions and a decrease in mean fetal weights (-10.6%) and in total live fetuses (19.4% below controls) was observed at the HDT. 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. External

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examination of fetuses revealed a missing tail in one HDT fetus, and agnathia (lower jaw), microstomia and anophthalmia in another fetus of a different HDT litter. Historical control data for missing tail for 1985-1988 indicate a low frequency for this effect. 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 same set of historical control data indicates that anophthalmia and decreased or absent jaw development has been observed only once in each of two studies [one study in 1986 and another in 1985].

Visceral examination of fetuses 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 compound-related; it was not listed in the historical control data, comprising 31 studies [4191 viscerally examined fetuses, and 763 litters] over the years 1985-1988. Skeletal examination revealed dose-dependent, statistically significant increases in several fetal frequencies and some litter frequencies of skeletal variations. 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).

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 control data 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%). 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 control data indicate that litter frequencies for this effect are in the range of 4.2-47.8%. 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. It is noted, however, that the historical control range 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, the fetal and litter incidences of dumbbell 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%). 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 which showed

litter incidences of up to 56.0-70.8% for supernumerary ribs.

The LOEL for developmental effects is 60 mg/kg/day (MDT) and the NOEL is 30 mg/kg/day.

5. Rat (Dermal Dosing)

Reference: Study for embryotoxic effects on rats after dermal administration. M. Renhof. August 30, 1988. Bayer AG. MRID 414508-01.

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 (nominal doses 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 PRC noted that higher dose levels may have been used as indicated by the absence of maternal toxicity. In addition, the slow absorption of this chemical by the dermal route suggests that plasma levels may not have plateaued until late in the period of organogenesis. The PRC noted that knowledge of a compound's pharmacokinetics was essential in the design of studies such as this and it recommended that additional information concerning pharmacokinetics following dermal administration in the rat be submitted.

6. Rabbit (Oral) Range Finding Study

Reference: Dose range-finding embryotoxicity study (including teratogenicity) with HWG 1608 TECHNICAL in the rabbit. February 4 1987. BAYER AG (Sponsor). RCC, research & Consulting Company AG and RCC, Switzerland (Testing Facility). MRID 407009-44.

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 or 300 mg/kg/day. Dams were sacrificed on day 28 of gestation for gross macroscopic observation of organs and removal of fetuses.

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 decreased 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. February 26 1987. BAYER AG (Sponsor). RCC, Switzerland (Testing Facility). MRID 407009-45.

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.

No compound related mortality or clinical signs of toxicity were reported at any dose level in the dams. 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%). Significantly reduced body weight gains were found between days 7 to 25 of gestation. Based on the above findings, the NOEL for maternal toxicity was 30 mg/kg/day and the LOEL was 100 mg/kg/day.

A statistically significant increase in fetal resorptions was observed at the HDT. This 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 vs controls (8.3%). The number of early resorptions in the HDT, although apparently increased with respect to controls, was not significantly increased.

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 one fetus with hydrocephalus internus in the HDT. Skeletal examination of fetuses revealed, in the HDT only, the occurrence of peromelia in 5 fetuses (4 litters) (See Table 1). The associated findings included humerus reduced in size, radius/ulna reduced in size or vestigial, forepaw reduced in size or absent. 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. Abnormal ossification and fusion of sternebra was reported in the LDT (1 fetus) and the MDT (1 fetus).

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.

8. Reproduction Study

Reference: HWG 1608, Two-generation study in rats. November 12, 1987. Mobay Corporation, (Sponsor). Bayer AG, Itingen, Switzerland (Testing Facility). MRID 407009-46

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.

There was an increase in the reported incidence of loss of hair in HDT FO adult females and in HDT and MDT F1B adult females. 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. 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. 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%, examination of the severity (grade) of the lesions indicates that HDT F0 females (grade 4 : 19/HDT vs 1/control) 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. 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

Table. 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)
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)
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.

effect, however, was not observed for F2a and F2b pups. Although there were statistically significant changes in viability and lactation indices for the F1a and F1b pups, these changes were not dose dependent, and did not occur in the F2a and F2b pups.

The NOEL for both systemic and reproductive toxicity was 300 ppm (equivalent to 15 mg/kg/day). The LOEL for parental toxicity was 1000 ppm. The LOEL for reproductive effects was based upon neonatal birth weight depression. Neonatal weights from birth through weeks 3 or 4 of lactation were consistently and significantly depressed at the high dose in all littering groups (F1a, F1b, F2a, and F2b). Although there was an apparent increase in the number of dead fetuses with respect to controls 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.

E. ADDITIONAL TOXICOLOGY DATA

1. Acute, Subchronic, and Chronic Toxicity Data

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

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

Administration of tebuconazole in the feed at concentrations of 100, 400, or 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. Adverse effects appeared to be more intense in females than in males and may be 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. 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, or 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.

Tebuconazole was administered to beagle dogs of both sexes at dietary concentrations of 0, 40, 200 or 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 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 both sexes 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. The dosing in this study may not have been adequate for the evaluation of carcinogenicity.

A mouse carcinogenicity 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 at 500 and 1500 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.

2. 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). Tebuconazole was negative in the Salmonella assay, the mouse micronucleus test, SCE and UDS.

Tebuconazole was negative in the following unacceptable assays: 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.

3. 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.

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.

F. Structure Activity Relationships

Tebuconazole is structurally related to the compounds listed in Figure 1. Maternal and developmental toxicity NOEL/LOEL values for these compounds are listed in Table 19. As shown in Table 19 bitertanol, propiconazole and hexaconazole and triademenol and uniconazole showed a developmental LOEL, below the maternal toxicity LOEL in rats. In addition, triadimefon, hexaconazole, and cyproconazole showed a developmental LOEL, below the maternal toxicity LOEL in rabbits.

Bitertanol was found to exhibit stunting and sternal anomalies, hexaconazole and uniconazole induced extra ribs, and propiconazole induced ossification retardation. 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).

G. Issues and Recommendations

1. Tebuconazole induces developmental toxicity in mice, rats and rabbits by the oral route of administration. Developmental toxicity is found at dose levels less than those that induces maternal toxicity or in the presence of slight maternal toxicity.

2. The NOEL for developmental toxicity in the mouse is 10 mg/kg/day based upon runting observed at higher dose levels. Equivocal maternal toxicity was observed at the highest dose tested (100 mg/kg). The PRC noted that higher dose levels could have been utilized in this study but, because prenatal toxicity was observed, the study was considered to be acceptable.

3. The NOEL for developmental toxicity in the dermal study in the mouse is 1000 mg/kg/day, the highest dose tested. Equivocal maternal toxicity was found at this dose level.

4. In the oral developmental toxicity study in the rat, the NOEL for developmental toxicity was found to be 30 mg/kg/day based upon increases in skeletal variations at dose levels of 60 mg/kg/day and greater.

5. No maternal or developmental toxicity was observed in the dermal study conducted in the rat. The lack of any indication of toxicity in this study and absence of a dermal penetration study using an appropriate vehicle led the PRC to question the design of this study. Additional information concerning pharmacokinetics and dermal absorption was requested to assist in the evaluation of this study.

6. The rabbit developmental toxicity study was considered to have an NOEL of 30 mg/kg/day for developmental toxicity based upon increases in variations and malformations at a dose level of 60 mg/kg.

7. Based upon neonatal birthweight depression, the NOEL for reproductive toxicity in the multigeneration reproduction study is 300 ppm (15 mg/kg/day). The NOEL for systemic toxicity is also 300 ppm in this study.

8. No further testing in the areas of reproductive or developmental toxicity was recommended by the PRC. As noted in item #5 above, further dermal absorption/pharmacokinetics investigation is recommended to assist in the interpretation of the rat dermal developmental toxicity study.

F. Summary

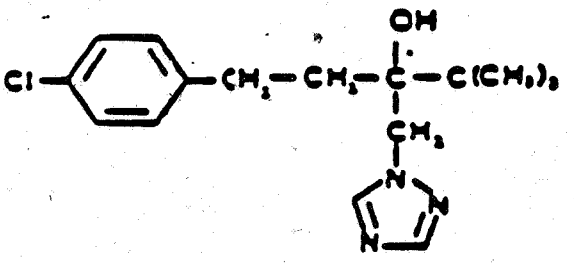
The Committee concluded that developmental toxicity was induced in mice, rats and rabbits via the oral route of administration. The lowest NOEL (10 mg/kg/day) is observed in mice. Equivocal maternal toxicity was observed at an oral dose level of 100 mg/kg in the mouse and at 30 mg/kg in the rat. Developmental toxicity was not induced in the rat or mouse at the highest dose tested via the dermal route (1000 mg/kg/day). Although each study conducted by the oral route of administration was considered to be acceptable by the PRC, additional pharmacokinetics information is suggested to verify that the study in rats conducted via the dermal route were adequately designed. Evidence of minimal maternal toxicity was found in the mouse dermal developmental toxicity study but no indication of developmental or maternal toxicity was found in the rat dermal developmental toxicity study.

Table 2. Maternal and Developmental Toxicity NOEL/LOEL Values for Structurally Related Compounds[a].

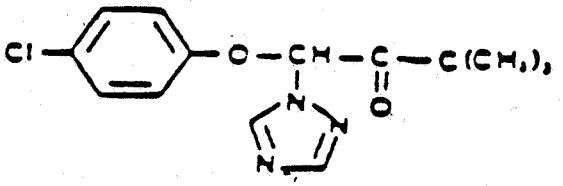
		Developmental Toxicity		
Chemical	Species	Maternal NOEL/LOEL (mg/kg/day)	Develop. NOEL/LOEL (mg/kg/day)	(CORE)[b] Remarks
Triadimefon	Rat	10/25	50/100	(M) Cleft palate
(Bayleton)	Rat	10/30	50/75	(M) Cleft palate
	Rabbit	>50 (HDT)	>50 (HDT)	(M) No effect reported at the HDT (50mg/kg/day).
	Rabbit	10/30	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.
	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.

Uniconazole[e]	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 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
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.

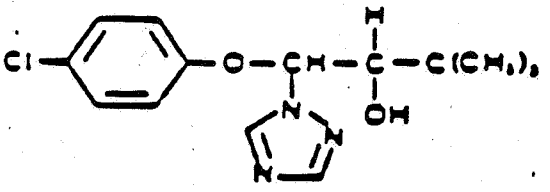
[a] Data obtained from the One-Liners for the indicated analogue. Invalid or Pilot studies were not selected.
[b] CORE = CORE Classification: G = Guideline, M = Minimum, S = Supplementary.
[c] EPA Peer Review Committee agreed on 9/7/90 that uniconazole should be classified a developmental toxicant. pair of ribs in 20/45 fetuses vs 14/112 in controls (p=2.8E-5). No NOEL or LOEL defined.



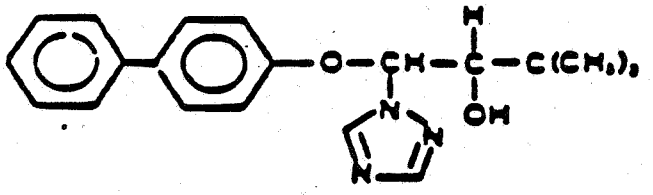
Terbuconazol
(Folicur)



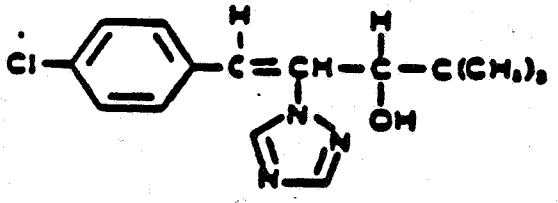
Triadimefon
(Bayleton)



Triademenol
(Baytan)

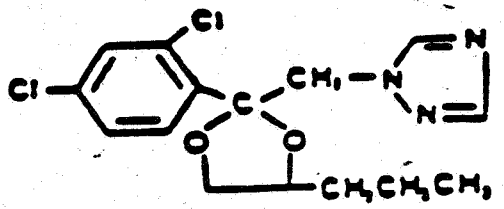


Bitertanol
(Baycor)

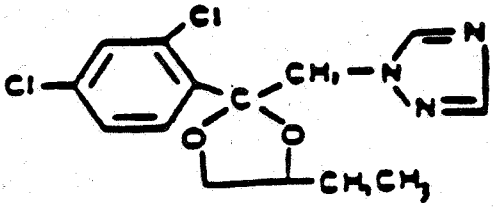


Uniconazole
(Prunit)

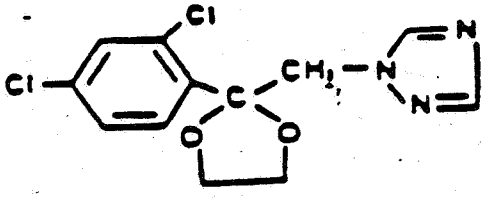
Figure 1. Tebuconazole and Structurally Related Compounds



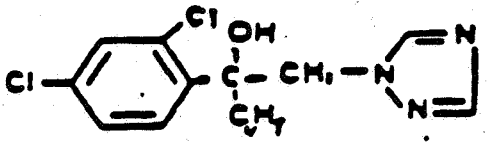
Propiconazole
(Tilt)



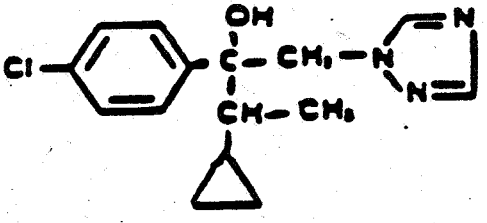
Etaconazole
(Vangard)



Azaconazole



Hexaconazole
(Anvil)



Cyproconazole
(SAN 619F)

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