HED DOC. NO. 012534

13-MAR-1998

MEMORANDUM

SUBJECT: ***TEBUCONAZOLE*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee,
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Rick Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)
and
Jess Rowland, Manager
Science Assessment Review Committees
Health Effects Division (7509C)

PC Code: 128997

The Health Effects Division (HED) FQPA Safety Factor Committee met on March 9, 1998 to determine the application of the FQPA Safety Factor to ensure the protection of infants and children from exposure to Tebuconazole as required by FQPA. The Committee's recommendations are attached.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that on the basis of comparative NOELs and LOELs, the data provided no indication of increased susceptibility of mice, rats or rabbits *in utero* and/or postnatal exposure to Tebuconazole. In the prenatal developmental toxicity studies in mice, rats, and rabbits, the NOELs for developmental toxicity were comparable or higher than the NOEL for maternal toxicity. However, the HIARC noted that although the maternal and developmental LOELs were the same in each study, there was more concern for the developmental effects at each LOEL. In all three species, at the LOEL, the developmental effects were pronounced even though the maternal toxicity was minimal (at the LOEL) and did not increase substantially in severity at higher doses. Additionally, the developmental effects were quite severe (including frank malformations) at higher doses in mice (100 mg/kg/day), rats (120 mg/kg/day), and rabbits (100 m g/kg/day). In the two-generation reproduction study, NOELs/LOELs were the same for offspring and parental systemic toxicity. For more information the reader is referred to the Report of the Hazard Identification Review Assessment Committee (*Memorandum:* J. Rowland to R. Loranger, dated March 3, 1998)

2. Adequacy of Database

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the HIARC determined that a postnatal developmental neurotoxicity study in rats is **required** based on the following weight-of-the-evidence considerations:

- In the developmental toxicity studies, there was evidence of alterations to the development of the fetal nervous system in mice (increased malformations of the brain and spinal column, and exencephaly, MRID No. 40821501 & 43776202), in rats (anophthalmia, MRID No. 40700943) and in rabbits (neural tubule defects characterized as meningocoele and spina bifida, and hydrocephalus, MRID No. 43776201 & 40700945). HIARC observed that effects on the nervous system of fetuses occurred only at doses of 100 mg/kg/day or higher--i.e., at doses at least 10-fold higher than the developmental toxicity NOEL (10 mg/kg/day) to be used for the assessment of acute dietary risk.

- Concern for Structure Activity Relationship. Tebuconazole is structurally related to Triadimefon (Bayleton), Triademenol (Baytan), Bitertanol (Baycor), Uniconazole (Prunit), Propiconazole (Tilt), Etaconazole (Vanguard), Azaconazole, Hexaconazole (Anvil), and Cyproconazole (SAN 619F). All of these compounds, except Etaconazole and Hexaconazole, have shown a developmental toxicity LOEL below the maternal toxicity LOEL in rats and/or rabbits.

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations

HED has previously concluded that the nature of the residue in plants is adequately understood (HED Metabolism Committee, 12/15/92). The residue of concern in plants is Tebuconazole per se, as specified in 40 CFR 180.474(a). Based on metabolism data available for peanuts, Tebuconazole is systemic.

The nature of the residue is adequately delineated in animal commodities (HED Metabolism Committee, 12/15/92). The residues of concern in animal commodities are the parent compound and its 1-(4-chlorophenyl)-4,4-dimethyl-3-(1-*H*-1,2,4-triazole-1-yl-methyl)-pentene-3,5-diol metabolite (HWG 2061), as specified in 40 CFR 180.474(b)(2).

Residues of Tebuconazole can transfer to meat/milk/poultry/eggs. HED has recommended tolerances for cattle (sheep, goat, hog) liver, kidney, meat byproduct, and milk.

A cursory inspection of the 1995 FDA monitoring database indicated 856 samples were analyzed for Tebuconazole. No detectable residues were reported. PDP does not monitor for Tebuconazole.

2. Drinking Water Exposure Considerations

Based on the present data file, Tebuconazole is persistent and relatively immobile. It is resistant to hydrolysis, aqueous photolysis, and soil metabolism, but slowly photodegraded on soil (half-life=191 days).

No monitoring data on Tebuconazole residues in ground water are readily available. Tebuconazole is not included in the Pesticides in Ground Water Database (USEPA, 1992), and it was not an analyte in the National Pesticide Survey (USEPA, 1990). Therefore, SCI-GROW4 modeling was conducted as the Tier I ground water assessment. GENEEC version 1.2 dated May 3, 1995 was used for the Tier 1 surface water analysis.

3. Residential Exposure Considerations

Chemical specific or site specific data are not available to assess residential exposure to Tebuconazole in paint products, therefore, the DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments were employed. The DRAFT SOPs normally rely on one or more upper-percentile assumptions and are intended to represent Tier 1 assessments.

The HED HIARC determined that there is no dermal endpoint for Tebuconazole (03/03/98).

Sufficient data/policies exist to adequately support the risk estimates and characterization for residential exposure to Tebuconazole.

III. RISK CHARACTERIZATION

1. Determination of the Factor

The Committee recommended that the **10x factor** for enhanced sensitivity to infants and children (as required by FQPA) should be **retained.**

2. Rationale for Selection of the FQPA Factor

- Although quantitatively no evidence of increased susceptibility was seen when the maternal and developmental NOELs and LOELs were compared, Tebuconazole has been shown to cause pronounced developmental effects in fetuses of all three species in the presence of minimal maternal toxicity, beginning at the LOEL.

- The developmental effects seen at the LOEL were corroborated with severe developmental effects at the next higher doses in all three species tested indicating that Tebuconazole is a potential developmental toxicant at higher doses.

- In the developmental toxicity studies, there was evidence of alterations to the development of the fetal nervous system in mice (increased malformations of the brain and spinal column, and exencephaly), in rats (anophthalmia), and in rabbits (neural tubule defects characterized as meningocoele and spina bifida, and hydrocephalus).

- Further corroborating this conclusion, Tebuconazole is structurally related to compounds that have been shown to cause developmental effects in rats at levels below the levels of maternal effects (Propiconazole, Hexaconazole, Triademenol, Uniconazole and Bitertanol). In rabbits, the developmental LOELs were lower than maternal LOEL for Triadimefon, Hexaconazole and Cyproconazole.

- Tebuconazole is structurally related to Triadimefon which is known to target the nervous system as a central stimulant, interfering with dopamine and has been used as a representative positive control chemical for findings of increased motor activity in standard neurotoxicity testing.

Therefore, the Committee decided to base the FQPA Safety Factor recommendation solely on the hazard (toxicological) considerations since each of the exposure assessments (dietary, drinking water, and residential) are Tier 1 and subject to further refinement. The

extent of the refinement and the degree of additional protectiveness (due to the use of conservative models and/or assumptions) will be described in the risk characterization which should be considered by the risk manager making the registration decision.

3. Identification of Population Subgroup

The Committee determined that the 10x factor is applicable for the following subpopulations:

Acute Dietary: Females 13 +, as well as Infants and Children. The FQPA factor is appropriate for these populations because the effects seen were developmental and are presumed to occur following "acute" exposures. The FQPA factor is not applicable to adult males.

Chronic Dietary: The FQPA factor is NOT applicable for chronic dietary exposure because: 1) the NOEL used in deriving the RfD is based on histopathological lesions of the adrenal glands in a chronic feeding study in dogs; 2) the NOEL selected is the lowest NOEL in the toxicology data base for Tebuconazole; 3) the developmental effects on which the FQPA factor is based were seen in pregnant animals of a different species (mice, rats, and rabbits); 4) maternal effects in these animals were minimal; and 5) the developmental effects are considered to be "acute" effects.

Residential Exposure: An FQPA factor is not applicable to these exposure scenarios since no hazard was identified via the dermal route and dermal risk assessments were not required. Risk via inhalation was considered to be negligible due to low vapor pressure and minimal potential for exposure to infants and children. Although occupational exposure is not considered when determining the FQPA safety factor, the factor should be considered when characterizing the risks to pregnant female workers exposed to the chemical.

SignOff Date:	3/13/1998
DP Barcode:	None
HED DOC Number:	012534
Toxicology Branch:	RAB1