

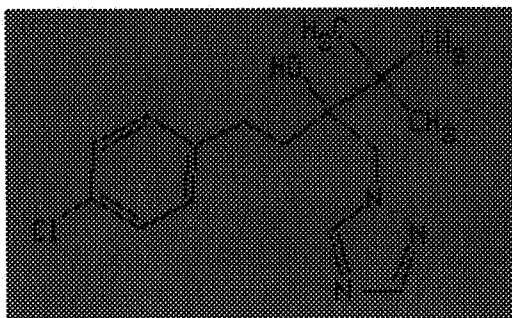
HED DOC. NO. 013628
Document dated 06/04/96

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Tebuconazole

PC Code: 128997

Structure:



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Tebuconazole at a meeting held on May 7, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: _____ Date: _____
(NAME)

SECTION HEAD: _____ Date: _____
(NAME)

BRANCH CHIEF: _____ Date: _____
(NAME)

DERMAL ABSORPTION DATA (If available)

MRID: 40995913

% absorbed: 49.9%

This value was obtained for an 8 hour exposure at a level of 0.604 $\mu\text{g}/\text{cm}^2$ of skin in the rat [MRID 40995913]. If required, values for other doses are available. It is noted that the study was conducted using ethanol as a solvent, which may lead to an overestimate of absorption.

ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: 83-3a

MRID No.: 40821501

Summary: In a developmental toxicity study (MRID No. 40821501) Tebuconazole (93.6% purity) in aqueous 0.5% Cremophor EL was administered to 25 NMRI/ORIG Kisslegg pregnant mice per dose by gavage at dose levels of 0, 10, 30 and 100 mg/kg/day from day 6 through 15 of gestation (GD 6-15). There were no overt signs of maternal toxicity. However, results from an associated study [Bayer Report 16511, T5025712, Lab. Proj. No. 97411, MRID No. 40821501] performed at dose levels of 0, 10, 20, 30, and 100 mg/kg/day administered at GD 6-15, tentatively indicated hepatic changes at all dose levels tested (increased release of AST, ALT, AP associated with liver weight increases and altered metabolism/physiology-increased mitosis, and lipidosis). There was also a reduction in hematocrit at dose levels of 20-100 mg/kg/day. **The maternal LOEL was 20 mg/kg/day based on the reduction of hematocrit. The maternal LOEL was 10 mg/kg/day.** These results from the associated study can be used to revise the maternal toxicity of the main study. 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 grams). In addition, the compound produced frank malformations (skull, "neural tube") at 100 mg/kg/day associated with a reduced rate of ossification in the cranium as compared to controls. **The Developmental LOEL is 30 mg/kg/day and is based upon an increased number of runts. The Developmental Noel is 10 mg/kg/day.**

Dose and Endpoint for use in risk assessment: 10 mg/kg/day; use the NOEL for developmental effects observed in NMRI mice. An increase in the number of runts (weight < 1.3 g) were observed at the LOEL of 30 mg/kg/day.

Comments about study and/or endpoint: This study was also recommended by the HED developmental PRC for acute dietary assessment in their meeting of May 7, 1992.

This risk assessment is required.

SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: None.

MRID No.: None.

Summary:: None.

Dose and Endpoint for use in risk assessment: Not applicable.

Comments about study and/or endpoint: No risk assessment required based on lack of maternal or developmental toxicity at the Limit Dose (1000 mg/kg/day) in dermal developmental toxicity studies in mice and rats.

This risk assessment is not required.

INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: None.

MRID No.: None.

Summary:: None.

Endpoint and Dose: Not applicable

Comments about dose/study: No risk assessment required based on lack of systemic effects at the Limit-Dose (1000 mg/kg/day) in a 21-day rabbit dermal toxicity study and dermal developmental toxicity studies in mice and rats.

- o In a 21-day dermal study with NZW rabbits [MRID 40700917] at 0, 50, 250, or 1000 mg/kg/day, the systemic NOEL was 1000 mg/kg/day.
- o In a Wistar rat dermal teratology study [MRID 41450801] at 0, 100, 300, or 1000 mg/kg/day on 25 cms², the NOEL for maternal or developmental toxicity was 1000 mg/kg/day.

- o In a NMRI mouse dermal teratology study [MRID 42010301 and HED PRC for Developmental Toxicity Report] at 0, 100, 300 or 1000 (10% b.s.), the NOEL for maternal or developmental toxicity was 1000 mg/kg/day.

This risk assessment is not required.

CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: None

MRID No.: None

Summary: None.

Dose and Endpoint for use in risk assessment: None.

Comments about study and/or endpoint: Not required since chronic exposure by this route is not of concern.

This risk assessment is not required.

INHALATION EXPOSURE (ANY TIME PERIOD):

Study Selected - Guideline No.: Not applicable.

MRID No.: 40700938

Summary: In a subacute inhalation toxicity study (MRID 40700938) Tebuconazole (96.2% a.i.) was administered to 10 Wistar Bor rats/sex/dose by head/nose only exposure at analytical concentrations of 0 (control air), 0 (control vehicle: 1:1 polyethylene glycol E40/ethanol), 1.2, 10.6, or 155.8 mg/m³/day [0, 0, 0.0012, 0.0106, or 0.1558 mg/l] for 15 daily 6-hour exposures over 3 weeks. At 1.2 or 10.6 mg/m³, there were no toxic signs or any effects on in-life parameters, on organ weights, or on gross or histologic findings. Exposure at 155.8 mg/m³ caused piloerection. There was also a moderate induction of liver O-demethylase in liver at the highest exposure level and a statistically significant of liver N-demethylase in both sexes. There were no effects of toxicological importance on clinical laboratory parameters or organ weights nor was there an increase in histological lesions. This study defined a LOEL of 155.8 mg/m³/day [0.1558 mg/l/day] based on

clinical signs and induction of liver microsomal enzymes. The NOEL was 10.6 mg/m³/day [0.0106 mg/l/day].

Dose and Endpoint for use in risk assessment: 10.6 mg/m³/day (0.0106 mg/l/day); the NOEL from a 3-week inhalation toxicity study (MRID 40700935) in Wistar Bor rats. The LOEL (155.8 mg/m³/day) was based on piloerection and induction of liver microsomal enzymes.

Comments about study and/or endpoint: None.

This risk assessment is required.

CANCER CLASSIFICATION AND BASIS:

Tebuconazole has been evaluated for carcinogenicity by the HED Carcinogenicity Peer Review Committee (CPRC) on May 26, 1993. The CPRC concluded that tebuconazole should be classified as group C - possible human carcinogen.

This decision was based on the statistically significant increase in the incidence of hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas in both sexes of NMRI mice both by positive trend and pairwise comparison at the HDT (1500 ppm) and the structural correlation with at least six other related triazole pesticides that produce liver tumors.

The CPRC recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

RfD AND Basis:

The Reference Dose (RfD) of tebuconazole is **0.01 mg/kg b.wt./day** based on a no-observed-effect-level (NOEL) of 1 mg/kg b.wt./day in dogs (for lenticular and corneal opacity and hepatotoxicity in a 1-year dog study) and an uncertainty factor of 100. A more recent 1-year dog study [MRID 420306-01 and 425372-01] defined a NOEL of 100 ppm (approx. 2.96 and 2.94 mg/kg b.wt./day in males and females, respectively). The review of this study has been transmitted to the RfD Committee for evaluation of its impact on the RfD of tebuconazole.

NOEL for critical study: 1 mg/kg b.wt./day in dogs (for lenticular and corneal opacity and hepatotoxicity)

Study Type - Guideline No.: 1-year chronic dog study. Guideline §83-1b.

MRID: 40700940

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Tebuconazole

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral (rat)	40700917	LD ₅₀ (fasted) = ♂: >5000 mg/kg ♀: 3933 mg/kg LD ₅₀ (unfasted) = ♂: 4264 mg/kg ♀: 3352 mg/kg	3
81-2	Acute Dermal (rat)	40700917 41290801	LD ₅₀ > 5000 mg/kg	4
81-3	Acute Inhalation	40700922	LC ₅₀ > 371 mg/m ³ , (Aerosol) LC ₅₀ > 5093 mg/m ³ , (Dust)	2
81-4	Primary Eye Irritation	40700917	Slightly irritating	3
81-5	Primary Skin Irritation	40700917	Nonirritant	4
81-6	Dermal Sensitization	40700928 41290802	No evidence of sensitization	-
81-8	Acute Neurotoxicity	-	-	-

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SignOff Date:
DP Barcode:
HED DOC Number:
Toxicology Branch:

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