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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 9/16/98

Subject: PP#6F4669 and PP#5F4577 - TEBUCONAZOLE PETITIONS FOR TOLERANCES FOR GRAPES AND GRASSES GROWN FOR SEED

DP Barcodes: D230515, D233490, D233509, and D241131 Caswell#: 463P
PRAT Case#: 286933, 287342 Chemical#: 128997
Submission#: S533972, S517950 40 CFR: 180.474
Class: Fungicide

Product names: Elite 45 DF Foliar Fungicide (EPA Reg. No. 3125-388), PP#6F4669
Folicur 3.6F (EPA Reg. No. 3125-394), PP#5F4577

To: M. Waller, PM Team 21
HB/RD (7505C)

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I. BACKGROUND

Bayer Corporation requests the establishment of permanent tolerances for residues of the fungicide tebuconazole [*alpha*-[2-(4-chlorophenyl)ethyl]-*alpha*-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol] in/on grapes at 5.0 ppm, grass forage at 8 ppm, grass hay at 25 ppm, and grass seed screenings at 55 ppm. Tolerances are established for residues of tebuconazole on various commodities ranging from 0.05 to 20 ppm (40 CFR 180.474).

II. EXECUTIVE SUMMARY

1. The toxicological database for tebuconazole is complete. After examining the data, however, the Hazard Identification Assessment Review Committee (HIARC) recommended that the registrant be required to perform and submit to the Agency a developmental neurotoxicity study (Guideline 83-6, OPPTS Guideline 870.6300). The lack of this study should not preclude establishment of the requested tolerances. Submission of the study, however, should be made a condition of the establishment of the tolerances.

2. For acute dietary risk assessment, the HIARC recommended that the No Observed Effect Level (NOEL) of 10 mg/kg/day for developmental effects observed in a developmental toxicity study in mice be used for risk assessment. An increased incidence of runts was observed at the Lowest Observed Effect Level (LOEL) of 30 mg/kg/day. The population subgroups of concern for this risk assessment are females (13+ years), infants, and children. No toxicological endpoint was identified by HIARC for the general population. An Uncertainty Factor of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the acute Reference Dose (RfD) for tebuconazole was calculated to be 0.10 mg/kg/day.

3. For chronic dietary risk assessment, the chronic RfD for tebuconazole is based on a 1-year chronic feeding study in dogs, in which the NOEL was 3.0 mg/kg/day and the LOEL was 4.4 mg/kg/day, based on histopathological changes in the adrenal gland (hypertrophy of the zona fasciculata and fatty changes in the zona glomerulosa in both sexes and lipid hyperplasia in the cortex in males). An Uncertainty Factor of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the chronic RfD for tebuconazole was calculated to be 0.030 mg/kg/day.

4. The Carcinogenicity Peer Review Committee determined that tebuconazole should be classified as a Group C - possible human carcinogen. For the purpose of carcinogenic risk assessment, the Committee recommended that the RfD approach should be used to estimate human risk.

5. Tebuconazole's registered residential uses are for the formulation of wood-based composite products, wood products for in-ground contact, plastics, exterior paints, glues and adhesives (Preventol A8 Preservative, EPA Registration No. 39967-13). **According to Mel Tolliver, of Bayer, the only residential end-use products currently on the market are for exterior "in-ground contact" wood**. [teleconference: S. Weiss (HED/RAB2), L. Sugiyama (RD/FB), M. Tolliver (Bayer) on 7/7/98]. Exposure via incidental ingestion (by children) and inhalation are not a concern for these products which are used outdoors. No paints or other end-use products containing tebuconazole are available for interior use. Thus, no risk assessment was conducted for residential exposure. **It should be noted that exposure data and risk assessments will be required for any future products that may result in inhalation and/or incidental ingestion (i.e. paints).**

6. No short-, intermediate-, or long-term dermal toxicity endpoints were identified. For short-,

intermediate-, and long-term inhalation toxicity, the NOEL of 0.0106 mg/L/day from a 21-day rat inhalation toxicity study was selected for risk assessment. The LOEL of 0.1558 mg/L/day was based on induction of liver microsomal enzymes and piloerection.

7. For acute dietary exposure, the FQPA Safety Factor Committee determined that the 10X safety factor for enhanced susceptibility of infants and children is applicable to the subpopulation females (13+ years) because the effects seen were developmental and are presumed to possibly occur following single exposures. Because a developmental neurotoxicity study (which includes 10 days of postnatal dosing) was required by the HIARC to be submitted to the Agency, the FQPA Safety Factor Committee determined that the 10X safety factor is also applicable to the subpopulations which include infants and children.

8. For chronic dietary exposure, the FQPA Safety Factor Committee determined that the 10X safety factor is not applicable. Application of the 10X safety factor to the acute RfD of 0.1 mg/kg/day results in an acceptable acute dietary exposure of 10% or less of the acute RfD for the subpopulations females (13+ years) and those that include infants and children.

9. The acute dietary (food only) risk assessment used the Monte Carlo analysis submitted in conjunction with PP#5F4577 (MRID No. 445646-01, dated 5/20/98). This analysis should be considered to be highly refined.

10. HED policy states that a factor of 3 will be applied to Generic Estimated Environmental Concentration (GENEEC) model values when determining whether or not a level of concern has been exceeded. If the GENEEC model value is less than or equal to 3 times the drinking water level of concern (DWLOC), the pesticide is considered to have passed the screen and no further assessment is needed. DWLOCs will be compared directly to SCI-GROW values (SOP for Drinking Water Exposure and Risk Assessments, 11/20/97). The acute DWLOC for the population subgroup females (13+ years) is 200 µg/L, and for infants/children is 14 µg/L . The surface water acute Estimated Environmental Concentration (EEC) is 14 µg/L (GENEEC peak value) and the ground water EEC is 0.3 µg/L [Screening Concentration in Ground Water (SCI-GROW) value] for tebuconazole. Despite the potential for exposure to tebuconazole in drinking water, HED does not expect the acute aggregate exposure to exceed 10% of the acute RfD. HED concludes that there is a reasonable certainty that no harm will result to females (13+ years), infants or children from acute aggregate exposure to tebuconazole residues.

11. For chronic dietary exposure, HED has estimated that chronic dietary exposure to tebuconazole from food only will utilize 12% of the chronic RfD for the population subgroup, U.S. Population, with the maximum utilized being 41% for children (1-6 years old). This is a conservative risk estimate because it is based on Theoretical Maximal Residue Concentration (TMRC) calculations, which assume 100% of all treated food and/or feed commodities having tebuconazole tolerances will contain tebuconazole residues at the tolerance level. HED generally has no concern for exposures below 100 percent of the chronic RfD (when the FQPA factor has been removed) because this RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health.

12. The chronic DWLOC for the U.S. Population (48 states) is 910 µg/L and for infants/children is 190 µg/L. These values are substantially higher than the surface water chronic EEC (10 µg/L, GENEEC 56 day average value) and the ground water EEC (0.3 µg/L, SCI-GROW value) for tebuconazole. Despite the potential for exposure to tebuconazole in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the chronic RfD. Under current HED guidelines, registered residential uses do not constitute a chronic exposure scenario. HED concludes that there is a reasonable certainty that no harm will result from chronic (non-cancer) aggregate exposure to tebuconazole residues.

13. Based on the HED Carcinogenicity Peer Review Committee recommendation that the RfD approach be used to estimate the carcinogenic risk to humans, a quantitative dietary cancer risk assessment was not performed. Risk concerns for carcinogenicity due to long-term consumption of tebuconazole residues are adequately addressed by the aggregate chronic exposure analysis using the chronic RfD.

14. Therefore, HED has no objections to the establishment of the tolerances for residues of tebuconazole listed in **Table 1.** A revised Section F listing all of these tolerances should be submited.

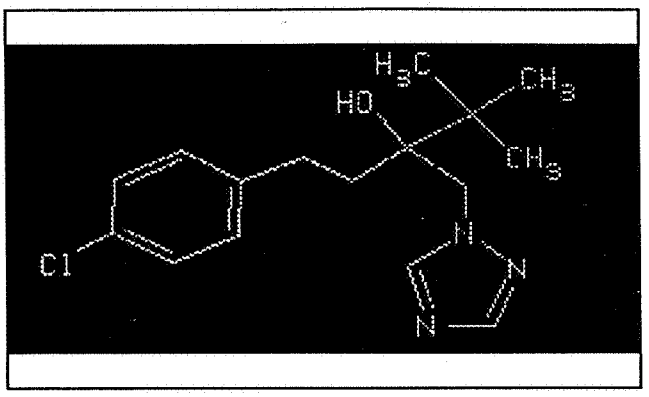
Table 1. Tolerances for residues of tebuconazole	
grapes	5 ppm
grass, forage	8 ppm
grass, hay	25 ppm
grass, seed screenings	55 ppm
grass, straw	30 ppm
milk	0.1 ppm
meat by-products of cattle, goats, horses, and sheep	0.2 ppm

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

1. Identification of Active Ingredient

The chemical structure of tebuconazole [*alpha*-[2-(4-chlorophenyl)ethyl]-*alpha*-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol] is as follows:



2. Product Chemistry

The product chemistry data requirements for technical grade tebuconazole have been satisfied. The petitioner has previously submitted product chemistry for technical grade tebuconazole in conjunction with PP#9F3724 (5/9/91 and 2/16/93, G. Otakie, CB NO. 5667 and D174886, respectively) and PP#3F4167 (10/25/94, G. Otakie, D201313). Based upon a Confidential Statement of Formula (CSF) dated 1/10/92, the technical product (EPA Reg. No. 3125-383) contains 96% tebuconazole.

ELITE 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) has been proposed for use on grapes (PP#6F4669). This product contains 45% by weight the active ingredient (ai) tebuconazole. FOLICUR 3.6F Fungicide (EPA Reg. No. 3125-394) has been proposed for use on grasses grown for seed (PP#5F4577). This product contains 3.6 lb ai/gallon.

B. Human Risk Assessment

1. Hazard Assessment

A listing of the toxicology studies required to support the amended registrations of Elite 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) and of Folicur 3.6F Fungicide (EPA Reg. No. 3125-394) and tolerances for residues of tebuconazole in/on grapes (PP#6F04669) and in/on grasses grown for seed (PP#5F04577) is presented in **Table 2.** All the required studies have been submitted and are acceptable except for a developmental neurotoxicity study in rats (Guideline

83-6, OPPTS Guideline 870.6300), which was required by the HIARC at a meeting on 2/17/98. The lack of this study at this time, however, should not preclude establishment of the requested tolerances. Nevertheless, submission of the study should be made a condition of the establishment of the tolerances.

A tabulated summary of acute toxicity studies on technical grade tebuconazole and the end-use formulations, Elite 45 DF and Folicur 3.6F, is presented in **Table 3.**

A tabulated summary of non-acute toxicity studies on technical grade tebuconazole is presented in **Table 4.**

Table 2. Toxicology Studies Required to Support Amended Registrations and Tolerances for Residues of Tebuconazole in/on Grapes and Grasses Grown for Seed

	REQUIRED	SATISFIED
TECHNICAL GRADE TEBUCONAZOLE		
§81-1 ACUTE ORAL TOXICITY - RAT	Y1	Y
§81-2 ACUTE DERMAL TOXICITY - RAT/RABBIT	Y	Y
§81-3 ACUTE INHALATION TOXICITY - RAT	Y	Y
§81-4 PRIMARY EYE IRRITATION - RABBIT	Y	Y
§81-5 PRIMARY DERMAL IRRITATION - RABBIT	Y	Y
§81-6 DERMAL SENSITIZATION - GUINEA PIG	Y	Y
§81-8 ACUTE NEUROTOXICITY - RAT	Reserved	N2
§82-1 90-DAY FEEDING - RAT	Y	Y
§82-1 90-DAY FEEDING - DOG	Y	Y
§82-2 21-DAY DERMAL - RAT/RABBIT	Y	Y
§82-4 SUBCHRONIC INHALATION - RAT	Y	Y
§82-7 90-DAY NEUROTOXICITY - RAT	Reserved	N2
§83-1 CHRONIC FEEDING - RAT	Y	Y3
§83-1 CHRONIC FEEDING - DOG	Y	Y
§83-2 CARCINOGENICITY - RAT	Y	Y3
§83-2 CARCINOGENICITY - MOUSE	Y	Y
§83-3 DEVELOPMENTAL TOXICITY - RAT	Y	Y
§83-3 DEVELOPMENTAL TOXICITY - RABBIT	Y	Y
§83-4 TWO-GENERATION REPRODUCTION - RAT	Y	Y
§83-6 DEVELOPMENTAL NEUROTOXICITY - RAT	Y4	N4
§84-2(a) GENE MUTATION	Y	Y
§84-2(b) STRUCTURAL CHROMOSOME ABERRATION	Y	Y
§84-4 OTHER GENOTOXIC EFFECTS	Y	Y
§85-1 GENERAL METABOLISM	Y	Y
END-USE FORMULATION (ELITE 45 DF)		
§81-1 ACUTE ORAL TOXICITY - RAT	Y	Y
§81-2 ACUTE DERMAL TOXICITY - RAT/RABBIT	Y	Y
§81-3 ACUTE INHALATION TOXICITY - RAT	Y	Y
§81-4 PRIMARY EYE IRRITATION - RABBIT	Y	Y
§81-5 PRIMARY DERMAL IRRITATION - RABBIT	Y	Y
§81-6 DERMAL SENSITIZATION - GUINEA PIG	Y	Y
END-USE FORMULATION (FOLICUR 3.6F)		
§81-1 ACUTE ORAL TOXICITY - RAT	Y	Y
§81-2 ACUTE DERMAL TOXICITY - RAT/RABBIT	Y	Y
§81-3 ACUTE INHALATION TOXICITY - RAT	Y	Y
§81-4 PRIMARY EYE IRRITATION - RABBIT	Y	Y
§81-5 PRIMARY DERMAL IRRITATION - RABBIT	Y	Y
§81-6 DERMAL SENSITIZATION - GUINEA PIG	Y	Y

1 Y = YES; N = NO

2 Not required at this time, but may be required at a later time.

3 Submitted as a combined chronic feeding/carcinogenicity study.

4 Required by the HED Hazard Identification Assessment Review Committee which met on 2/17/98. The lack of this study at this time should not preclude establishment of the requested tolerances. Submission of this study, however, should be made a condition of the establishment of the tolerances.

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Table 3. Acute Toxicity of Technical Grade Tebuconazole and the End-Use Formulations, Elite 45 DF and Folicur 3.6F

Guideline	Study Type	Species	Dose (Purity)	Results
			Technical	
81-1	Acute Oral	Rat	500-5000 mg/kg (Tech. 97.1% purity)	LD50 (fasted): ♂: >5000 mg/k LD50 (unfasted): ♂: 4264 mg/k
81-2	Acute Dermal	Rat	1000-5000 mg/kg (Tech. 97.1% purity)	LD50 : ♂ & ♀: > 500
81-3	Acute Inhalation	Rat	0.371 mg/L (wet aerosol) (Tech. 96.2% purity)	LC50 (4-hours, wet aerosol): (No deaths)
81-4	Primary Eye Irrit.	Rabbit	(Tech. 96.3% purity)	Mildly irritatin
81-4	Primary Eye Irrit.	Rabbit	(Tech 97.1% purity)	Slightly irriratin
81-5	Primary Dermal. Irrit.	Rabbit	(Tech. 97.1% purity)	Non irritant
81-5	Primary Dermal Irrit.	Rabbit	(Tech. 96.6% purity)	Non irritant
81-6	Dermal Sensitization	Guinea pig	25% in aqueous Cremophor (Tech. 97.4% purity)	No evidence of skin sensiti the Buehler test
			Formulation: ELITE 45 DF	
81-1	Acute Oral	Rat	(46.2% a.i.)	LD50 (fasted): ♂: 4865 mg/kg;
81-2	Acute Dermal	Rabbit	(46.2% a.i.)	LD50: > 2000 mg/kg
81-3	Acute Inhalation	Rat	(45.3% a.i.)	LC50 (4 hours): > 0.
81-4	Primary Eye Irrit.	Rabbit	(46.2% a.i.)	Irritation cleared within 7
81-5	Primary Dermal Irrit.	Rabbit	(46.2% a.i.)	Not a primary dermal
81-6	Dermal Sensitization	Guinea pig	(45% a.i.)	Positive when tested by t topical closed patch test

Table 3. (Cont.) Acute Toxicity of Technical Grade Tebuconazole and the End-Use Formulations, Elite 45 DF and Folicur 3.6F

			Formulation: Folicur 3.6 F	
81-1	Acute Oral	Rat	(38.7% a.i)	LD50 (fasted): ♂: 4184 mg/kg;
81-2	Acute Dermal	Rabbit	(38.7% a.i)	LD50: > 2000 mg/kg
81-3	Acute Inhalation	Rat	(38.7% a.i.)	LC50 (4 hours): > 1.
81-4	Primary Eye Irrit.	Rabbit	(38.7% a.i.)	Not irritating
81-5	Primary Dermal Irrit.	Rabbit	(38.7% a.i.)	Not a primary dermal
81-6	Dermal Sensitization	Guinea pig	(38.7% a.i.)	Negative when tested by t topical closed patch test

Table 4. Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	Res
-	Feed. 4 week	Rat (Wistar)	Oral gavage	0, 30, 100 or 300 mg/kg/day for 28 days plus 28 days recovery. (Tech., 97.0% purity)	NOEL = 30 mg/kg/day. mg/kg/day , based on he clinical chemistry chang
-	Feed. 30 day	Dog (Beagle)	In diet	0, 500 or 5000 ppm for 30 days. (Tech., 93.4% purity)	NOEL = 500 ppm. LE on elevated alkaline pho study.
-	Feed. 8 week	Mice	In diet	0, 500 or 2000 ppm for 8 weeks and 0, 125, 500, or 2000 ppm for 5 days. (Tech., 96.9% purity) Range finding study for carcinogenicity.	NOEL < 500 ppm (8 w NOEL < 125 ppm (5 d Systemic toxicity (8 wee increased absolute and r associated with increase vacuolization, and lipido Microsomal enzymes (5 at all dose levels. Doses carcinogenicity study we ppm.
82-1 (a)	Feed. 3 month	Rat (Wistar)	In diet	0, 100, 400 or 1600 ppm for 13 weeks. M: 0, 8, 34.8 or 171.7 mg/kg/day; F: 0, 10.8, 46.5 or 235.2 mg/kg/day (Tech., 93.4% purity)	♂: NOEL = 400 ppm (3 = 1600 ppm (171.7 mg/ decreased body weight adrenal vacuolation and ♀: NOEL = 100 ppm (1 LEL: 400 ppm (46.5 mg adrenal vacuolation.
82-1 (b)	Feed. 3 month	Dog (Beagle)	In diet	0, 200, 1000 or 5000 ppm for 13 weeks. M: 0, 74, 368 or 1749 mg/kg/day; F: 0, 73, 352 or 1725 mg/kg/day (Tech. 93.4% purity)	NOEL = 200 ppm (73 1000 ppm (352 mg/kg/d body weight and body food consumption *N*-demethylase activity. ♂ and 1 ♀; cat

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
82-2	Dermal 3 week	Rabbit (NZW)	Dermal	0, 50, 250 or 1000 mg/kg/day, 5 days/week for 3 weeks. (Tech. 97.1% purity)	No signifi NOE
82-4	Inhalation 3 week	Rat (Wistar)	Inhalation	0, 0.0012, 0.0106 or 0.1558 mg/L/day; 6 hour /day for 3 weeks. 15 expos. (Tech., 96.2% purity)	NOEL = 0.010 mg/L/day, base liver *N*-demethy
83-1 (a) & 83-2(a)	Combined Chronic Feed/Carcino-genicity Study (2-years)	Rat [Bor:WISW (SPF Cpb)]	In diet	0, 100, 300 or 1000 ppm (♂: 5.3, 15.9 or 55 mg/kg/day; ♀: 7.4, 22.8 or 86.3 mg/kg) for 2 years. (Tech. approx. 95% purity)	♂: NOEL = 10 ppm (15.9 mg/ ♀: NOEL = 10 ppm (22.8 mg/ depression; dec corpuscular vol hemoglobin con enzymes. Not carcinogeni
83-1 (b)	1-year Chronic Feeding (1987)	Dog (beagle)	In diet	0, 40, 200 or 1000 (1-39 wk) & 2000 ppm (40-52 wk) for 1 year. M&F: 0, 1, 5 or 25/50 mg/kg/day (Tech. 96.9% purity)	NOEL = 40 p (5 mg/kg/day), corneal opacit appearance of t

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
83-1 (b)	1-year Chronic Feeding (1989)	Dog (beagle)	In diet	0, 100 or 150 ppm for 1 year; (♂: 0, 3.0 or 4.4 mg/kg/day; ♀: 0, 3.0 or 4.5 mg/kg/day). (Tech. 96.0% purity)	NOEL: 100 ppm (3.0 (4.4 mg/kg/day), bas sexes. In males there w fasciculata cells amoun 0/4 at 100 ppm and in c in males included glomerulosa (3/4) and (2/4) at 150 ppm vs. 1/ and control dogs. In fe zona fasciculata cells of 150 ppm and to 0/4 at Fatty changes in the zo adrenal amounted to 2/ ppm an **This study was used to for tebuconazole. With factor of 100, and a N the chronic RfD of tebu mg/kg/day.**
83-2(b)	Carcinogenicity (21 Months) (1988)	Mice (NMRI)	In diet	0, 20, 60 or 180 ppm for 21 months; (♂: 5.9, 18.2 or 53.1 mg/kg/day; ♀: 9.0, 26.1 or 80.5 mg/kg/day (Tech. 95.1% purity)	The compound was n tested. Adequate leve were not achieved. T resulted in slight liver to weight, associated wit vacuolation and lipid cortical size and hyperp inters

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
83-2(b)	Carcinogenicity (91-Weeks) (1991)	Mice (NMRI)	In diet	0, 500 or 1500 ppm for 91 weeks; (♂: 0, 84.9 or 279 mg/kg/day; ♀: 0, 103.1 or 365.5 mg/kg/day) (Tech. 96.2% purity)	Statistically significant decr food consumption were rep decreased food efficiency a at 1500 ppm in females. C (dose-dependent increases i Phosphatase) for both sexes effects at both 500 ppm an increases reached statistical 1500 ppm in males and at 1 Histopathology included do panacinar fine fatty vacuola 500 and 1500 ppm in males Other histopathology includ proliferation in both sexes ovarian atrophy that was st 1500 ppm. Maximum Tole at or around 500 ppm. Ne of statistically significant in neoplasms: adenomas (35.4 1500 ppm in males and car ppm in females.
83-3	Developmental Toxicity	Rat (Wistar)	Oral (gavage)	0, 10, 30 or 90 mg/kg/day, days 6-15 of gestation. Range finder. (Tech. 98.2% purity).	Minimally toxic at the HD body weight. Doses select 120 mg/kg/day.

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
83-3	Developmental Toxicity	Rat (Wistar)	Oral (gavage)	0, 30, 60 or 120 mg/kg/day, days 6-15 of gestation. (Tech. 98.3% purity)	Maternal NOEL: 30 mg/k mg/kg/day, (based on ele liver weights. Developme Developmental LEL: 60 ossification of thoracic, ce sternum, limbs and an inc
83-3	Developmental Toxicity	Rat (Wistar)	Dermal	0, 100, 300 or 1000 mg/kg/day, on a 25 cm2 area, 6 hour/day, days 6-15 of gestation. (Tech. 97.4% purity)	Maternal and Developme Maternal and Developme No maternal or developm dose level.
83-3	Developmental Toxicity	Rabbit (Chinchilla)	Oral (gavage)	0, 30, 100 or 300 mg/kg/day, days 6-18 of gestation. (Tech. 98.2% purity).	Range Finder. Mater Maternal LEL: 300 mg/ weight gain and 100% pr selected for main stu m
83-3	Developmental Toxicity	Rabbit (Chinclilla)	Oral (gavage)	0, 10, 30 or 100 mg/kg/day, days 6-18 of gestation. (Tech. 98.2% purity).	Maternal NOEL: 30 mg/k mg/kg/day, (based on a m weight gains and food con NOEL: 30 mg/kg/day. mg/kg/day, [based on inc frank malformations in 8 f peromelia in 5 fetuses/4 li litter), hydrocephalus and
83-3	Developmental Toxicity	Mice (NMRI/ORIG)	Oral (gavage)	0, 10, 20, 30 or 100 mg/kg/day, days 6-15 of gestation. (Tech. 97.4% purity).	Maternal toxicity (vacuola and Alkaline Phosphatase) Reduction in MCV in par occurred at doses $\geq$ 20 m target organ. Maternal N LOEL: 20 mg/kg/day

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
83-3	Developmental Toxicity	Mice (NMRI/ORIG)	Oral (gavage)	0, 10, 30 or 100 mg/kg/day, days 6-15 of gestation. (Tech. 93.6% purity).	Maternal NOEL: 10 mg mg/kg/day, based on a c study (also MRID 40821 toxic effects in the subje NOEL: 10 mg/kg/day. mg/kg/day, based on the runts (weight < 1.3 g).
83-3	Developmental Toxicity	Mice (NMRI/ORIG)	Dermal	0, 100, 300 or 1000 mg/kg/day, 6 hour/day, 10% of body surface, d. 6-15 of gestation. (Tech. 98.1% purity)	Maternal NOEL: 1000 Developmental NOEL: No evidence of maternal study. However a comp dosing protocol, also M apparent maternal NOE LOEL of 300 mg/kg (ba increased liver enzyme l significant increases in f variations coupled to ma incidences (e.g. bipartite increased to 40% at the developmental NOEL an and 1000 mg/kg/day. The HED Peer Review developmental and repro (5/7/92) that the tentativ mg/kg/day in mice be ch The PRC also concluded equivocal maternal toxic

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
83-3	Developmental Toxicity	Mice (NMRI/ORIG)	Dermal	0, 100, 300 or 1000 mg/kg/day, 6 hour/day, 10% of body surface, days 6-15 of gestation. (Tech. 96.0% purity)	Companion study Liver microsomal 0.01) elevated at highest dose teste in the liver at the increased in dose significantly elev 100 mg/kg/day, liver histopathol Also see results f
83-4	2 Generation Reproduction	Rat (Wistar)	In diet	0, 100, 300 or 1000 ppm for 2 generations. males and females: 0, 5, 15 or 50 mg/kg/day (Tech. 95.2% purity).	Maternal NOEL: LEL: 1000 ppm (body weights, inc decreased liver a NOEL: 300 ppm 1000 ppm (50 m body weights fro
84-2	Mutagenicity Ames test	Salmonella sp.	-	37.5-2400 ηg/plate. (Tech. 96.6% purity)	Non mutagenic
84-2	Mutagenicity HGPRT	CHO cells	-	12.5-2000 ηg/plate (No cytotoxicity). (Tech. 96.6% purity).	Non mutagenic
84-2	Mutagenicity Dominant lethal	Mice	-	2000 mg/kg, only one dose. No positive controls. (Tech. 93.5% purity).	
84-2	Mutagenicity Micronucleus Assay	Mice	-	200, 500 or 2000 mg/kg. (Tech. 95.3% purity).	
84-2	Mutagenicity S. Chr. Exch.	CHO cells	-	Tech. 96.5% purity.	Negative with me without metabolic
84-2	Mutagenicity In vitro cytogenetics.	Human lymphocytes	-	30-300 ηg/mL (no cytotoxicity without activation). (Tech . 96.5% purity).	Negative wit

Table 4. (Cont.) Toxicity Summary of Technical Grade Tebuconazole (Non-Acute Studies)

Guideline	Study Type	Species	Route	Dose	
84-2	Mutagenicity DNA damage/repair	E.Coli	-	625-1000 ŋg/plate (no growth inhibition zone demonstrated). (Tech. 97.1% purity).	Negative with or wi
84-2	Mutagenicity Unscheduled DNA synthesis	Rat primary hepatocytes	-	0.504-25.2 ŋg/mL. (Tech. 96.5% purity).	
85-1	Metabolism	Rat	I.V. & oral (Gavage)	1 or 20 mg/kg [phenyl-14C] > 99% purity or [triazole 3,5-14C] > 98.4% purity Tech. non-labeled 99.5% purity.	98.1% of the oral dose i dose excreted in urine a dosing. At sacrifice (72 residue (- GI tract) amou total of 10 compounds id fraction of the identified successive oxidation step material. At the higher detoxication patterns ma
85-2	Dermal penetration	Rat	Dermal	Triazole 3,5-14C] > 99.66% purity Tech. non-labeled 94.7% purity. Solvent used: ethanol	In rats dosed dermally at 52.4 and 547 ŋg/cm2, t 24 hours amounted to 27 of the applied dose, resp remained on the applicat wash increased with dos 24.7, 24.40, 32.02 and doses, respectively. The by 8 hours was 49.9% a ŋg/cm2. Solvent (ethan of absorption.

2. Dose/Response Assessment

The HIARC met on 2/17/98 to evaluate the toxicology data base for tebuconazole with special attention to the developmental, reproductive and neurotoxicity data. These data were re-reviewed specifically to characterize the toxicological hazard to infants and children and to address the sensitivity of infants and children to tebuconazole as required by the Food Quality Protection Act (FQPA). In addition, the HIARC re-affirmed the toxicological endpoints and doses previously selected by the TES Peer Review Committee for acute dietary exposure risk assessments and for short-, intermediate-, and long-term occupational/residential exposure risk assessments. The HIARC also re-affirmed the chronic RfD previously established by the RfD Peer Review Committee. The TES Peer Review Committee met on 5/7/96 and the RfD Peer Review Committee on 3/5/91 and 4/4/96. In addition, the FQPA Safety Factor Committee met on 3/9/98 to determine the application of the FQPA safety factor to ensure the protection of infants and children from exposure to tebuconazole as required by the FQPA.

a. Special Sensitivity of Infants and Children

Under the FQPA, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential prenatal and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children.

(1) Meeting of the HED Developmental/Reproductive Toxicity Peer Review Committee

The Developmental/Reproductive Toxicity Peer Review Committee met on 5/7/92 to discuss and evaluate the developmental and reproductive toxicity of tebuconazole. The Committee concluded that developmental toxicity was induced in mice, rats and rabbits via the oral route of administration, but was not induced in mice or rats at the highest dose tested (1000 mg/kg/day) via the dermal route of administration. Since the lowest NOEL for developmental toxicity was observed in mice, the Committee recommended that the NOEL for developmental toxicity in the oral mouse study (10 mg/kg/day) be used for assessment of acute dietary risk. This recommendation was re-affirmed by the HIARC on 2/17/98.

(2) Adequacy of Database

The toxicology data base for tebuconazole includes an acceptable 2-generation reproduction study in rats (MRID 40700946); oral prenatal developmental toxicity studies in mice (MRID 40821501, 43776202), rats (MRID 40700943) and rabbits (MRID 40700945, 43776201); a dermal prenatal developmental toxicity study in mice (MRID 42010301) and a dermal prenatal developmental toxicity study in rats (MRID 41450801; supplementary study). These studies meet the standard toxicology data requirements, as required for a food-use chemical, in 40 CFR Part 158. However, after evaluation of the findings in these studies, particularly with respect to effects on the fetal nervous system, together with a consideration of neurotoxic effects observed in several other developmental toxicity studies on structurally related triazole fungicides, the HIARC recommended that the registrant be required to perform and submit to the Agency a developmental neurotoxicity study in rats (Guideline 83-6, OPPTS Guideline 870.6300).

(3) Determination of Susceptibility

On the basis of NOELs and LOELs, the HIARC determined there was no indication of increased susceptibility of the offspring of mice, rats or rabbits to prenatal or postnatal exposure to tebuconazole. In the prenatal developmental toxicity studies, NOELs for maternal toxicity were equivalent to NOELs for developmental toxicity and in the 2-generation reproduction study in rats, the systemic (parental) NOEL also was equivalent to the reproductive (pup) NOEL. The HIARC, however, did note that maternal effects observed in the prenatal developmental toxicity studies at the LOEL were of minimal concern and did not increase substantially in severity at higher doses, whereas the developmental effects at the LOEL and at higher doses were considerably more pronounced. At the higher doses, the developmental effects were severe (including frank malformations) in mice (100 mg/kg/day), rats (120 mg/kg/day) and rabbits (100 mg/kg/day).

(4) Summary of Available Neurotoxicity Data

No acute or subchronic neurotoxicity studies on rats or hens are available for tebuconazole, but in a battery of subchronic and chronic studies, as required for a food-use chemical, there were no indications of treatment-related effects on the central or peripheral nervous system of experimental animals. No clinical signs, changes in brain weights, gross necropsy results or histopathological results indicated any part of the nervous system to be a target organ for tebuconazole. In the prenatal developmental toxicity studies, however, the HIARC did note several effects on the fetal nervous system. These effects included alterations in 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). The 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. The HIARC also noted that tebuconazole is structurally related to several other triazole fungicides which have demonstrated a developmental toxicity LOEL below the maternal toxicity LOEL in rats and/or rabbits. These compounds include triadimefon, triadimenol, bitertanol, uniconazole, propiconazole, azaconazole and cyproconazole.

(5) Recommendation for a Developmental Neurotoxicity Study

On the basis of the findings described above in the prenatal developmental toxicity studies on mice, rats and rabbits, together with a consideration of effects observed in several other developmental toxicity studies on structurally related triazole fungicides, the HIARC recommended that the registrant be required to perform and submit to the Agency a developmental neurotoxicity study (Guideline 83-6, OPPTS Guideline 870.6300).

(6) FQPA (10X) Safety Factor

The HED FQPA Safety Factor Committee, which met on 3/9/98, recommended that the 10X safety factor for enhanced sensitivity to infants and children, as required by FQPA, be retained. This recommendation was based on the following considerations: 1) the pronounced developmental effects observed in fetuses of mice, rats and rabbits in the presence of minimal maternal toxicity; 2) evidence of alterations in the development of the fetal nervous system in mice, rats and rabbits; and 3) the structural relationship of tebuconazole to several other triazole fungicides which have been shown to cause developmental effects in rats and/or rabbits at dose levels below those producing maternal effects. The Committee further determined the the 10X safety factor is applicable to acute dietary risk assessments for females (13+ years) because the effects seen were developmental and are presumed to possibly occur following single exposures. The Committee determined that the 10X safety factor also is applicable to infants and children because a developmental neurotoxicity study (which includes 10 days of postnatal dosing) was required by HIARC to be submitted to the Agency, thus indicating a concern for potential neurotoxic effects following postnatal exposure to tebuconazole.

b. Chronic Reference Dose (RfD)

The RfD Peer Review Committee met on 3/5/91 and 4/4/96 to evaluate toxicology data submitted in support of tebuconazole registrations with particular emphasis on the long-term, carcinogenicity, reproductive and developmental toxicity of the compound. The RfD Peer Review Committee recommended that the chronic RfD for tebuconazole be based on a 1-year chronic feeding study in dogs (MRID 42030601, 42537201) in which the NOEL was 100 ppm (2.96 mg/kg/day in males and 2.94 mg/kg/day in females) and the LOEL was 150 ppm (4.39 mg/kg/day in males and 4.45 mg/kg/day in females), based on histopathological changes in the adrenal gland (hypertrophy of the zona fasciculata in both sexes, fatty changes in the zona glomerulosa in both sexes and lipid hyperplasia in the

cortex in males). An Uncertainty Factor of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the chronic RfD for tebuconazole was calculated to be 0.03 mg/kg/day. This chronic RfD was re-affirmed by the HIARC on 2/17/98.

c. Carcinogenic Classification and Risk Quantification

The Carcinogenicity Peer Review Committee, which met on 5/26/93, concluded that tebuconazole should be classified as a Group C - possible human carcinogen. This conclusion was based on results in a 91-week carcinogenicity study in NMRI mice (MRID 42175001, 42469301) in which the following effects were observed : 1) a statistically significant increase in the incidence of hepatocellular adenomas, carcinomas and combined adenomas/carcinomas in male mice both by positive trend and pairwise comparison at the highest dose tested (279 mg/kg/day); and 2) a statistically significant increase in the incidence of hepatocellular carcinomas and combined adenomas/carcinomas in female mice both by positive trend and pairwise comparison at the highest dose tested (366 mg/kg/day). The structural relationship of tebuconazole to at least six other triazole fungicides that also produce hepatocellular tumors in male and/or female mice supported the Committee's conclusion. These compounds include triadimefon, triadimenol, uniconazole, propiconazole, cyproconazole and etaconazole. For the purpose of carcinogenic risk assessment, the Committee recommended that the Reference Dose (RfD) methodology be used to estimate human risk.

d. Dermal Absorption

In a rat dermal absorption study (MRID 40995913), the percent dermal absorption for an 8 hour exposure to tebuconazole at a dose of 0.604 ug/sq cm of skin was determined to be 49.9%. The study was conducted using ethanol as the solvent, which may have led to an overestimate of the percent absorption.

e. Summary of Doses and Toxicological Endpoints for Use in Human Risk Assessment

(1) ACUTE DIETARY (ONE DAY)

Study selected: Developmental Toxicity Study, Mice (Guideline 83-3)
MRID: 40821501

Summary: In a developmental toxicity study in mice, technical grade tebuconazole (93.6% purity) in aqueous 0.5% Cremophor EL was administered to 25 pregnant NMRI mice per dose by gavage at dose levels of 0, 10, 30 or 100 mg/kg/day from day 6 through 15 of gestation (GD 6-15). There were no overt signs of maternal toxicity in this study. However, results from an associated study (MRID 40821501) in which tebuconazole was similarly administered at dose levels of 0, 10, 20, 30 or 100 mg/kg/day on GD 6-15, indicated hepatic changes (increased AST, ALT and alkaline phosphatase, increased liver weights, hyperplasia and lipidosis). There was also a reduction in hematocrit at dose

levels of 20-100 mg/kg/day. The maternal toxicity LOEL in the associated study was determined to be 20 mg/kg/day based on the reduction of hematocrit. The maternal toxicity NOEL was 10 mg/kg/day. These results from the associated study were used to revise the maternal toxicity endpoints in the main study. In the main study, developmental toxicity was noted at the mid- and high-dose levels as retarded growth and increased numbers of runts (fetuses weighing less than 1.3 grams). In addition, at 100 mg/kg/day, tebuconazole induced frank malformations (in the skull, brain and spinal column) and a reduced rate of ossification in the cranium as compared to controls. The developmental toxicity LOEL was 30 mg/kg/day and is based upon an increased number of runts. The developmental toxicity NOEL was 10 mg/kg/day.

Dose and endpoint for use in risk assessment: NOEL = 10 mg/kg/day (the NOEL for developmental effects observed in NMRI mice). An increase in the number of runts (fetuses weighing less than 1.3 grams) was observed at the LOEL of 30 mg/kg/day.

Comments about study and/or endpoint: The HIARC (2/17/98) determined this dose and endpoint should be used for assessing the acute dietary risk for the subpopulation females (13+ years) because the effects seen were developmental and are presumed to possibly occur following single exposures. Subsequent to this, the FQPA Safety Factor Committee (3/9/98) determined that this dose and endpoint should also be used for assessing the acute dietary risk for infants and children because a developmental neurotoxicity study (which includes 10 days of postnatal dosing) was required by HIARC to be submitted to the Agency, thus indicating a concern for potential neurotoxic effects following postnatal exposure to tebuconazole. A dose and endpoint were not identified by the HIARC for the general population.

This risk assessment is required for the subpopulations females (13+ years), infants and children.

(2) CHRONIC DIETARY (RfD Study)

Study Selected: 1-Year Chronic Feeding Study, Dogs (Guideline 83-1b)
MRID: 42030601, 42537201

Summary: In a chronic feeding study in beagle dogs, technical grade tebuconazole was administered in the diet to 4 dogs/sex/dose for 1 year at dose levels of 0, 100 or 150 ppm (equivalent to 0, 2.96 and 4.39 mg/kg/day in males and 0, 2.94 and 4.45 mg/kg/day in females). At 150 ppm, treatment-related histopathologic effects in the adrenal cortex were observed. Hypertrophy of the zona fasciculata (males and females), fatty changes in the zona glomerulosa (males and females) and lipid hyperplasia (males only) were noted. The LOEL in this study is 150 ppm (about 4.4 mg/kg/day in males and females), based on histopathologic effects in the adrenal glands. The NOEL is 100 ppm (about 3.0 mg/kg/day in males and females).

Dose and endpoint for use in risk assessment: NOEL = 3.0 mg/kg/day in males and females. Treatment-related histopathological effects in the adrenal gland were observed at

the LOEL of 4.4 mg/kg/day in males and females. An Uncertainty Factor of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the chronic RfD for tebuconazole was calculated to be 0.030 mg/kg/day.

Comments about study and/or endpoint: This study was a follow-up to a previously conducted 1-year feeding study in beagle dogs (MRID 40700940) in which the NOEL was 40 ppm (1 mg/kg/
day) and the LOEL was 200 ppm (5 mg/kg/day), based on ocular lesions (corneal and lens opacity) and liver toxicity in both sexes.

This risk assessment is required for all populations.

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

Dermal Exposure

Study Selected: None.
MRID: None.

Summary: None.

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

Comments about study and/or endpoint: This risk assessment is not 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 and the lack of systemic effects at the limit dose (1000 mg/kg/day) in a 21-day dermal toxicity study in rabbits.

In a dermal developmental toxicity study in mice (MRID 42010301), tebuconazole was administered dermally to pregnant mice on days 6-15 of gestation at dose levels of 0, 100, 300 or 1000 mg/kg/day. The test material was applied to shaved skin for 6 hours/day. No toxicologically significant maternal toxicity or developmental toxicity was observed in the study at the highest dose tested (1000 mg/kg/day).

In a dermal developmental toxicity study in rats (MRID 41450801), tebuconazole was administered dermally to pregnant rats on days 6-15 of gestation at dose levels of 0, 100, 300 or 1000 mg/kg/day. The test material was applied to shaved skin for 6 hours/day. No maternal toxicity or developmental toxicity was observed in the study at the highest dose tested (1000 mg/kg/day).

In a 21-day dermal toxicity study in rabbits (MRID 40700937),

tebuconazole was administered dermally at dose levels of 0, 50, 250 or 1000 mg/kg/day. No systemic toxicity was observed at the highest dose tested (1000 mg/kg/day).

This risk assessment is not required.

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

Dermal Exposure

Study Selected: None.
MRID: None.

Summary: None.

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

Comments about study and/or endpoint: This risk assessment is not required, based on lack of maternal or developmental effects in dermal developmental toxicity studies in mice (MRID 42010301) and rats (MRID 41450801) at the limit dose (1000 mg/kg/day) and lack of systemic effects at the limit dose (1000 mg/kg/day) in a 21-day dermal toxicity study in rabbits (MRID 40700937).

This risk assessment is not required.

(5) LONG-TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Dermal Exposure

Study Selected: None.
MRID: None.

Summary: None.

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

Comments about study and/or endpoint: This risk assessment is not required, based on lack of maternal or developmental effects in dermal developmental toxicity studies in mice (MRID 42010301) and rats (MRID 41450801) at the limit dose (1000 mg/kg/day) and lack of systemic effects at the limit dose (1000 mg/kg/day) in a 21-day dermal toxicity study in rabbits (MRID 40700937).

This risk assessment is not required.

(6) INHALATION EXPOSURE (ALL TIME PERIODS):

Study Selected: 21-Day Inhalation Study, Rats (Guideline: 82-4)
MRID: 40700938

Summary: In a 21-day subchronic inhalation toxicity study, technical grade tebuconazole (96.2% purity) was administered to 10 Wistar rats/sex/dose by nose only exposure at analytical concentrations of 0 (control air), 0 (control vehicle: 1:1 polyethylene glycol E40/ethanol), 0.0012, 0.0106 or 0.1558 mg/L/day for 15 6-hour exposures over 3 weeks. At 0.0012 and 0.0106 mg/L/day, there were no toxic signs or effects on clinical laboratory parameters, organ weights, or gross or histopathologic findings. Exposure at 0.1558 mg/L/ day produced piloerection. There was also a moderate induction of liver *O*-demethylase and a statistically significant induction of liver *N*-demethylase in both sexes at 0.1558 mg/L/day. The LOEL in this study was 0.1558 mg/L/day based on piloerection and induction of liver microsomal enzymes. The NOEL was 0.0106 mg/L/day.
Dose and endpoint for use in risk assessment: NOEL = 0.0106 mg/L/day, the NOEL from a 21-day inhalation toxicity study in Wistar rats. The LOEL of 0.1558 mg/L/day was based on piloerection and induction of liver microsomal enzymes.

Comments about study and/or endpoint: This dose and endpoint should be used for short-term, intermediate-term and long-term inhalation exposure risk assessments, when applicable.

This risk assessment is required.

Table 5. Summary of Doses and Toxicological Endpoints for Use in Human Risk Assessment

osure Duration	Exposure Route	Toxicological Endpoint		Comments
		Dose	Effect	
ute	Dietary	NOEL = 10 mg/kg/day. UF = 100. Acute RfD = 0.10 mg/kg/day.	At LOEL of 30 mg/kg/day, increase in number of runts was observed.	Developmental toxicity study in mic (MRID 40821501)

ronic	Dietary	NOEL = 3.0 mg/kg/day. UF = 100. Chronic RfD = 0.030 mg/kg/day.	At LOEL of 4.4 mg/kg/day, histopathological effects in the adrenal gland (hypertrophy, fatty changes, and lipid hyperplasia) were noted.	1-year chronic feeding study in dog (MRID 42030601 and 42537201)
rt-, Intermediate-, Long-Term cupational/ idential	Dermal	None	None	Risk assessment not required based on lack of toxicity at th limit dose (1000 mg/kg/day) in derm developmental toxicity studies in mice and rats (MRI 42010301 and 41450801) and lack of toxicity at the lim dose (1000 mg/kg/day) in a 21-day dermal toxicity study in rabbits (MRID 40700937)
rt-, Intermediate-, Long-Term cupational/ idential	Inhalation	NOEL = 0.0106 mg/L/day	AT LOEL of 0.1558 mg/L/day, induction of liver microsomal enzymes and piloerection.	21-day inhalation study in rats (MRID 40700938)

cer		Group C (possible human carcinogen)--no Q1* (Use RFD Approach). Based on: 1) a statistically significant increase in the incidence of hepatocellular adenomas, carcinomas and combined adenomas/carcinomas in male NMRI mice both by positive trend and pairwise comparison at the highest dose tested; 2) a statistically significant increase in the incidence of hepatocellular carcinomas and combined adenomas/carcinoma in female NMRI mice both by positive trend and pairwise comparison at the highest dose tested; and 3) the structural relationship of tebuconazole to at least six other structurally related triazole fungicides that also produce hepatocellular tumors in male and/or female mice. The Carcinogenicity PRC recommended that for the purpose of carcinogenic risk characterization, the Reference Dose (RfD) approach should used for quantification of human cancer risk.

3. Exposure and Risk Assessment/Characterization

a. Occupational and Residential Exposure and Risk Assessment

(1) Occupational Exposures & Risks

Occupational exposure and risk assessment estimates for the application of tebuconazole on grass grown for seed and grapes are summarized in **Table 5**. Worker exposure estimates are based on surrogate data from the Pesticide Handlers Exposure Database (PHED) as presented in the PHED Surrogate Exposure Guide (PSEG, 5/97). Estimated inhalation MOEs are greater than 100 for all mixer/loader and applicator scenarios and therefore do not exceed HED's concern.

There is potential for dermal exposure during mixing/loading, application, and postapplication activities. However, the HIARC did not select dermal endpoints of concern and stated that a risk assessment for dermal exposure is not required (HIARC meeting on 2/17/98).

The exposure estimates for mixer/loader and applicator are based on central tendency estimates of the unit exposure, area treated, and body weight, and a central to upper-percentile assumption for the application rate and are considered to be representative of central tendency exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data and assumptions regarding amount of chemical handled. These estimated exposure levels are believed to be reasonable central tendency to high-end estimates based on observations from surrogate field studies and professional judgement.

Per the Worker Protection Standard (WPS), the minimum level of PPE is based on the

acute toxicity of the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with WPS.

The restricted entry interval (REI) of 12 hours on the Elite 45 DF Foliar Fungicide and Folicur 3.6F Fungicide labels is in compliance with the WPS.

(2) Residential and Other Non-Occupational Exposures and Risks

Tebuconazole's registered residential uses are for the formulation of wood-based composite products, wood products for in-ground contact, plastics, exterior paints, glues and adhesives (Preventol A8 Preservative, EPA Registration No. 39967-13). According to Mel Tolliver, of Bayer, the only residential end-use products currently on the market are for exterior in-ground contact wood. [teleconference: S. Weiss(HED/RAB2), L. Sugiyama (RD/FB), M. Tolliver (Bayer) on 7/7/98]. Exposure via incidental ingestion (by children) and inhalation are not a concern for these products which are used outdoors. No paints or other end-use products containing tebuconazole are available for interior use. Thus, no risk assessment was conducted for residential exposure. It should be noted that exposure data and risk assessments will be required for any future products that may result in inhalation and/or incidental ingestion (i.e. paints).

Table 5. Exposure and Risk Assessment for Occupational Mixe					
Worker Activity	Personal Protective Equipment	Inhalation UE1 (µg/lb ai handled)	UE Data Confidence Level	Percent Inhalation Absorption	Applicat Rate (lb ai/
Grass Grown For Seed (FOLICUR 3.6F Fungicide /EPA Reg.					
Ground: Mixer/Loader 2	Single Layer with Gloves	1.2	High	100	0.225
Ground: Applicator3	Single Layer with Gloves	0.74	Medium	100	0.225
Aerial: Mixer/Loader2	Single Layer with Gloves	1.2	High	100	0.225
Aerial: Applicator4	Single Layer without Gloves	0.068	Medium	100	0.225
Grapes (ELITE 45 DF Foliar Fungicide /EPA Reg. No. 3					
Ground: Mixer/Loader 5	Single Layer with Gloves	0.77	High	100	0.112
Ground: Applicator6	Single Layer with Gloves	4.5	High	100	0.112
Aerial: Mixer/Loader5	Single Layer with Gloves	0.77	High	100	0.112
Aerial: Applicator4	Single Layer without Gloves	0.068	Medium	100	0.112

1Unit Exposure (UE) from Pesticide Handlers Exposure Database (PHED),Version 1.1, PHED Surrogate Exposure Guide (PSEG) 05/97

2PHED Scenario used: Mixer/Loader (ALL LIQUID FORMULATIONS, OPEN MIXING)

3PHED Scenario used: Ground Applicator (GROUNDBOOM, OPEN CAB)

4PHED Scenario used: Aerial Applicator (LIQUID FORMULATIONS, ENCLOSED COCKPIT)

5PHED Scenario used: Mixer/Loader (DRY FLOWABLE FORMULATIONS, OPEN MIXING)

6PHED Scenario used: Ground Applicator (AIRBLAST, OPEN CAB)

7Average Daily Dose (ADD) = PHED unit exposure (µg/lb ai handled) x (0.001 mg/µg) x % absorption x application rate (lb ai/A) x acres treated/day ÷ body wt (kg)

8Inhalation MOE = NOEL/ADD where the Inhalation NOEL for any time period = 0.0106 mg/L. This concentration was converted to a dose as follows:

[0.0106 mg/L (NOEL) x 8.46 L/hr (Wistar rat inhalation rate) x (6 hr/day rat exposure duration)] ÷ 0.187 kg (Wistar rat body weight) = **2.9 mg/kg/day**

Taken from the HED Tebuconazole Risk Assessment 9-16-98

b. Dietary Exposure and Risk Assessment/Characterization

1) Exposure from Food Sources

Tolerances are established under 40 CFR §180.474(a) for residues of the fungicide tebuconazole in or on bananas at 0.05 ppm, barley forage, hay and straw at 0.10, barley grain at 0.05 ppm, cherries at 4.0 ppm, oat forage, hay and straw at 0.10 ppm, oat grain at 0.05 ppm, peaches (includes nectarines) at 1.0 ppm, peanuts at 0.1 ppm, peanut hulls at 4.0 ppm, wheat forage, hay, and straw at 0.10 ppm, and wheat grain at 0.05 ppm.

Time-limited tolerances, for Section 18 emergency exemptions, are established under 40 CFR §180.474(b)(1) for residues of the fungicide tebuconazole in or on barley grain at 2.0 ppm, barley hay and straw at 20 ppm; pistachios at 1.0 ppm, wheat hay at 15 ppm, and wheat straw at 2.0 ppm. Time-limited tolerances, for Section 18 emergency exemptions, are established under 40 CFR §180.474(b)(2) for residues of the fungicide tebuconazole in or on milk at 0.1 ppm; cattle, goats, hogs, horses, poultry, and sheep meat byproducts at 0.2 ppm.

(a) GLN 860.1200: Directions for Use

ELITE 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) is to be applied to grapes for the control of powdery mildew and black rot at a rate of 4 ounces of product per acre (0.1125 lbs ai/A) per application. For powdery mildew, the product is to be applied before bloom (at 2 to 8 inches of new cane growth) and may be repeated at 10 to 14 day intervals. During berry sizing, the product may be applied at 7 to 10 day intervals. For black rot, the first application may be made at 1 to 3 inches of new cane growth and continue through 5° Brix stage or until veraison (berry coloring) is complete. A maximum of 2 lbs of product (0.9 lbs ai/A) may be applied per season. A 14 day pre-harvest interval (PHI) is specified.

FOLICUR 3.6F Fungicide (EPA Reg. No. 3125-394) is to be applied to grasses grown for seed when grasses are in active growth. Up to 4 applications can be made at rates ranging from 0.11 to 0.22 lb ai/A/application. The total amount applied in a season cannot exceed 0.45 lb ai/A. Label restrictions include do not forage, cut green chop, or use seed for feed purposes. Regrowth may be grazed starting 118 days after last application. Maintain a 10 to 14 day interval between applications. Folicur should not be applied within 5 days of harvest.

(b) GLN 860.1300: Nature of the Residue - Plants

HED has previously concluded the nature of the residue in plants is adequately understood (HED Metabolism Committee, 12/15/92). The metabolism of tebuconazole in/on grapes, wheat, and peanuts has been discussed in reviews of PP#9G3817 (C.Olinger, 6/8/90) and PP#9F3724 (G.Otakie, 5/9/91 and 2/16/93). The residue of concern in plants is tebuconazole per se, as specified in 40 CFR 180.474(a).

(c) GLN 860.1300: Nature of the Residue - Animals

The nature of the residue in ruminants and poultry is adequately delineated (HED Metabolism Committee, 12/15/92, see also PP#9F3724, G. Otakie, 5/9/91 and 2/16/93). 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)-pentane-3,5-diol metabolite (HWG 2061), as specified in 40 CFR 180.474(b)(2).

(d) GLN 860.1340: Residue Analytical Methods

An enforcement method (GLC/NPD, Bayer Method 101341, MRID No. 42909801) for the determination of residues of tebuconazole in crops has undergone a successful Petition Method Validation by ACL/BEAD (E. Hayes, 6/10/93) and has been sent to the FDA for inclusion in PAM II.

The gas chromatographic method entitled "An Analytical Residue Method for the Determination of Tebuconazole and HWG 2061 Residues in Bovine and Poultry Tissues, Milk and Eggs" (MRID #42209510) is adequate for enforcement purposes for the combined residues of tebuconazole and HWG 2061 in animal commodities (G.Otakie, 3/31/94, PP#9F3724).

The data gathering method used to support the magnitude of the residue in grapes study is discussed in HED's memo *Tebuconazole in/on Grapes. Evaluation of Analytical Methodology and Residue Data (PP#6F04669, DP* D227017, *W. Wassell, 8/13/96)*. This method differs slightly from the plant enforcement method (omits GPC cleanup specified in the enforcement method). The method was deemed adequate for data collection purposes.

The enforcement method was used as the data gathering method to support the magnitude of the residue in grasses study. Recoveries were adequate for grass forage. See HED's memo *Section 3 Registration and Permenant Tolerance for Use of Tebuconazole Grasses Grown for Seed* (*PP#5F4577*, DP D220455, G. Herndon, 8/7/96) for additional details. Recovery data for grass seed screenings and straw are discussed in the 9/18/98 HED review (M. Doherty, Barcode D248847).

(e) GLN 860.1360: Multiresidue Methods

The petitioner has previously submitted data concerning the recovery of tebuconazole and its t-butylhydroxy metabolite by the FDA Multiresidue Methods of PAM I. Residues of tebuconazole and its t-butylhydroxy metabolite are not recoverable by these methods.

(f) GLN 860.1380: Storage Stability Data

The petitioner has submitted data that show residues of tebuconazole are stable during

frozen storage in/on grapes for 30 months and grape pomace (dry), grape juice, and raisin waste for 28 months (PP#9F3724/9F3818, G. Otakie, 6/15/94, D198515). HED has previously concluded that these data are adequate to support the grape magnitude of the residue study (see HED's memo *Tebuconazole in/on Grapes. Evaluation of Analytical Methodology and Residue Data, PP#6F04669, DP* D227017, *W. Wassell, 8/13/96)* The grass forage samples were held (frozen) up to 720 days from harvest to analysis. A storage stability study that was conducted on wheat commodities showed that tebuconazole was stable in wheat forage samples when stored frozen for up to 30 months (914 days). These data are adequate to cover the grass samples. Straw and seed screenings were stored for 853 days and 946 days respectively.

(g) GLN 860.1500: Crop Field Trials

Details concerning the field trials for grapes can be found in HED's memo *Tebuconazole in/on Grapes. Evaluation of Analytical Methodology and Residue Data (PP#6F04669, DP* D227017, *W. Wassell, 8/13/96)* . HED concludes the geographic representation of the major grape growing regions of the U.S. in the submitted field trials is adequate. HED also concludes residue levels of tebuconazole in/on grapes are not expected to exceed 5.0 ppm when ELITE 45 DF Foliar Fungicide is applied as proposed in the subject petition. The submitted residue data support the proposed tolerance level of 5.0 ppm for residues of tebuconazole in/on grapes.

Details concerning the field trials for the forage and hay of grasses grown for seed can be found in HED's memo *Section 3 Registration and Permenant Tolerance for Use of Tebuconazole Grasses Grown for Seed (PP#5F4577*, DP D220455, G. Herndon, 8/7/96). In summary, residues of tebuconazole are not expected to exceed 8 ppm in grass forage and 25 ppm in grass hay as a result of the proposed use of FOLICUR 3.6F Fungicide. Tolerances for grass seed screenings and grass straw are needed at 55 ppm and 30 ppm, respectively, since these feed items have been returned to Table 1 of Guideline 860.1000 (see 9/14/98 HED memo, M. Doherty)

(h) GLN 860.1520: Processed Food/Feed

Details concerning the grape processing study can be found in HED's memo *Tebuconazole in/on Grapes. Evaluation of Analytical Methodology and Residue Data (PP#6F04669, DP* D227017, *W. Wassell, 8/13/96)* . HED concludes tolerances for residues of tebuconazole in/on raisins and grape juice are not required for the proposed use. No processed commodities are associated with grass.

(i) GLN 860.1480: Meat, Milk, Poultry, and Eggs

No poultry or swine feed items are associated with this use of tebuconazole; therefore, dietary burdens for poultry and swine were not calculated. Based on dietary compositions derived from OPPTS 860.1000 Table 1 (9/96) and the proposed tolerances for grass grown for seed in conjunction with established tolerances for residues of tebuconazole on

other livestock feed items, a theoretical cattle diet was created resulting in a tebuconazole Maximum Theoretical Dietary Burden (MTDB) of approximately 40 ppm. This diet assumes that all items in the diet contain residues of tebuconazole and that those residues exist at the level of the tolerance. These assumptions result in a highly conservative, worst-case exposure of cattle to tebuconazole and HED takes these assumptions into account in estimating residue levels in livestock commodities.

The 28-day tebuconazole feeding study on dairy cattle (MRID No. 422095-18) used residue levels of 0, 30, 90, and 300 ppm in the diet. With the inclusion of grass seed screenings, the MTDB exceeds the 30-ppm dosing level. However, based on the pattern of results in the cattle feeding study, the value of the MTDB in relation to the 30-ppm feeding level, the unrealistic nature of the diet composition, and the extremely conservative estimate that all dietary residues occur at the level of the tolerance, HED does not expect the residues in animal commodities to exceed those levels previously recommended. **Therefore, HED recommends that tolerances for animal commodities be set at 0.2 ppm for meat by-products of cattle, goats, horses, and sheep and at 0.1 ppm for milk.** The registrant should submit a revised Section F proposing such tolerances at those levels.

Cattle fat and meat tolerances should not be needed as a result of the proposed use on grasses.

(j) GLN 860.1400: Water, Fish, and Irrigated Crops - Not Applicable.

(k) GLN 860.1460: Food Handling - Not Applicable.

(l) GLN 860.1850: Confined Accumulation in Rotational Crops

Grapes are not rotated crops and HED has previously concluded that due to the nature of the chemical (fungicide) and the nature of the registration for grass (grasses grown for seed only), rotational crops will not be an issue (see HED's memo *Section 3 Registration and Permenant Tolerance for Use of Tebuconazole Grasses Grown for Seed, PP#5F4577*, DP D220455, G. Herndon, 8/7/96).

(m) GLN 860.1900: Field Accumulation in Rotational Crops - Not applicable.

(n) Tolerance Reassessment Summary - Not applicable.

(o) Codex Harmonization

A Codex MRL is proposed (Step 5) for residues of tebuconazole in/on grapes at 2.0 ppm. There are no established or proposed tolerances for tebuconazole in or on grapes in Canada and Mexico. Tolerance compatibility problems do not exist with respect to Mexico or Canada, but do exist with respect to the Codex MRL. As HED has concluded

the submitted residue data support a U.S. tolerance level of 5.0 ppm for tebuconazole in/on grapes, it is not possible to harmonize the proposed tolerance for residues of tebuconazole in/on grapes with Codex. HED suggests the petitioner consider providing all relevant studies to Codex once the U.S. tolerance is established in order that the Codex MRL may be amended to accommodate U.S. use needs.

There are no CODEX, Canadian, or Mexican MRLs established for residues of tebuconazole in/on grass.

2) Risk From Food Sources

(a) Acute Dietary Risk (Acute RfD = 0.10 mg/kg/day)

For acute dietary exposure, the FQPA Safety Factor Committee determined that the 10X safety factor is applicable to the subpopulations females (13+ years), as well as infants and children because the effects seen were developmental and are presumed to occur following "acute" exposures.

Application of the 10X safety factor to the Acute RfD of 0.10 mg/kg/day results in an acceptable acute dietary risk of 10% or less of the Acute RfD for the subpopulations females (13+ years), infants and children.

The acute dietary (food only) risk assessment used the Monte Carlo analysis submitted in conjunction with PP#5F4577 (MRID Nos. 445646-01, dated: 5/20/98). A detailed review of the analysis was performed by HED (see 8/21/98 memo, W. Wassel, DP Barcode 248264). The following assumptions were utilized in the Monte Carlo analysis:

- percent crop treated data were used for all commodities;

- maximum residue levels from crop field trials for single serving commodities such as bananas and peaches were utilized;

- average residue levels from crop field trials were used for blended commodities such as fruit juices, grains and oils;

-anticipated residue levels for ruminant commodities were calculated using a livestock diet constructed using anticipated residue levels for livestock feed items.

This analysis should be considered highly refined. This analysis was run with 2000 iterations. The results of the Monte Carlo analysis are summarized in **Table 6.**

Table 6. Acute Dietary Exposure Analysis by Monte Carlo

Population Subgroup	Exposure (99.9th Percentile) (mg/kg/day)	Percent Reference Dose 1, 2 (%RfD)
Nursing Infants (<1 year)	0.0067	6.7%

Non-nursing Infants (<1 year)	0.0074	7.4%
Children (1 to 6 years)	0.0086	8.5%
Children (7 to 12 years)	0.0033	3.3%
All Infants (<1 year)	0.0070	7.0%
Females (13 years plus)	0.0033	3.3%

1 Percentage reference dose (% RfD) = (Exposure/RfD) X 100%

2 Allowable % RfD is ≤ 10%.

(b) Chronic, Non-Carcinogenic Risk (Chronic RfD = 0.03 mg/kg/day)

The chronic dietary (food only) risk assessment was perfromed with the Dietary Exposure Evaluaion Model (DEEM) using the USDA 1989-91 Continuing Survey of Food Intake by Individuals (CSFII). The existing tebuconazole tolerances (published, pending, and those proposed in these petitions) result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the percentages of the RfD listed in Table 7.

In conducting this chronic dietary risk assessment, HED has made very conservative assumptions -- 100% of grapes and grasses grown for seed and all other commodities having tebuconazole tolerances will contain tebuconazole regulable residues and those residues will be at the level of the tolerance -- which result in an overestimation of human dietary exposure. Thus, in making a safety determination for these tolerances, HED is taking into account this conservative exposure assessment.

Table 7. Chronic Dietary Exposure Analysis by the DEEM System

Population Subgroup	Exposure (mg/kg/day)	Percent Reference Dose 1, 2 (%RfD)
U.S. Population (48 States)	0.0037	12%
Nursing Infants (<1 year old)	0.0056	19%
Non-Nursing Infants (<1 year old)	0.011	37%
Children (1-6 years old)	0.012	41%
Children (7-12 years old)	0.0045	15%
U.S. Population (summer season)	0.0040	13%
U.S. Population (autum season)	0.0045	15%
Midwest Region	0.0038	13%
Western Region	0.0049	16%
Pacific Region	0.0054	18%
Females (13+/nursing)	0.0057	19%
Non-Hispanic Whites	0.0038	13%
Non-Hispanic Other than Black or White	0.0040	13%

1 Percentage reference dose (% RfD) = (Exposure/RfD) X 100%

2 Allowable % RfD is ≤ 100%.

The subgroups listed above are: (1) the U.S. Population (48 states); (2) those for infants and children; and, (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

(c) Chronic, Carcinogenic Risk

Based on the HED Cancer Peer Review Committee recommendation that the RfD approach be used, a quantitative dietary cancer risk assessment was not performed. Dietary risk concerns due to long-term consumption of tebuconazole residues are adequately addressed by the DEEM chronic exposure analysis using the RfD.

3) Exposure from Drinking Water Sources

Based on present data in the EFED files, tebuconazole is persistent and relatively immobile (EFED Memo, G. Maske, 4/22/98, D243244). There are no established Maximum Contaminant Level or health advisory levels for residues of tebuconazole in drinking water (5/13/98, personal communication, EPA Safe Drinking Water Hotline, 800-426-4791).

The following information concerning residues of tebuconazole in ground and surface waters were provided to HED by EFED (Memo, G. Maske, 4/22/98, D243244).

(a) Ground Water

Monitoring data for residues of tebuconazole in ground water are not 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).

EFED used its SCI-GROW (Screening Concentration in Ground Water) screening model and environmental fate data to determine the estimated concentration for tebuconazole in ground water. SCI-GROW is an empirical model based upon actual ground water monitoring data collected for the registration of a number of pesticides that serve as benchmarks for the model. The current version of SCI-GROW appears to provide realistic estimates of pesticide concentrations in shallow, highly vulnerable ground water sites (i.e., sites with sandy soils and depth to ground water of 10 to 20 feet).

Ground Water EEC: 0.3 µg/L (for both chronic and acute analysis, based upon use rate for almonds and pistachios)

(b) Surface Water

EFED used its GENEEC (Generic Estimated Environmental Concentration) screening model and environmental fate data to determine the EECs for tebuconazole in surface water. GENEEC is used to estimate pesticide concentrations in surface water for up to 56

days after a single runoff event. GENEEC simulates a 1 hectare by 2 meters deep edge-of-the-field farm pond which receives pesticide runoff from a treated 10 hectare field. GENEEC provides an upper-bound concentration value. GENEEC can substantially overestimate (by a ≥ 3-fold factor) true pesticide concentrations in drinking water.

Surface Water Acute EEC: 14 µg/L (peak) (Value is based on usage rate for almonds and pistachios)

Surface Water Chronic EEC: 10 µg/L (avg 56-day concentration) (Value is based on use rate for almonds and pistachios.)

HED policy states that a factor of 3 will be applied to GENEEC model values when determining whether or not a level of concern has been exceeded. If the GENEEC model value is ≤ 3 times the drinking water level of concern (DWLOC), the pesticide is considered to have passed the screen and no further assessment is needed. DWLOCs will be compared directly to SCI-GROW values (SOP for Drinking Water Exposure and Risk Assessments, 11/20/97).

4) Risk From Drinking Water Sources

For purposes of risk assessment, the maximum EECs for tebuconazole in drinking water (14 ppb in surface water, [GENEEC peak value] and 10 µg/L in surface water, [GENEEC 56-day average value]) should be used for comparison to the back-calculated human health drinking water levels of concern (DWLOC) for acute and chronic (non-cancer and cancer) endpoints, respectively. These DWLOCs for various population categories are summarized in the **Tables 8 and 9.**

Table 8. Drinking Water Levels of Concern for ACUTE Exposure (using Food Exposure from Monte Carlo Analisis)

Population Category5	Acute RfD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure1 (mg/kg/day)	DWLOC 2,3,4 (µg/L)
Females (13+ years old)	0.1	0.0033	0.0067	200
Infants/Children	0.1	0.0086	0.0014	14

1Maximum Water Exposure (Acute) (mg/kg/day) = Acute RfD (mg/kg/day) ÷ 10 - Food Exposure (mg/kg/day)
2DWLOC(µg/L) = Max. water exposure (mg/kg/day) * body wt (kg) ÷ [(10-3 mg/µg) * water consumed daily (L/day)]
3Default body weights for Females (13+ years old) = 60 kg, Children= 10 kg
4HED Default Daily Drinking Rates are 2 L/day for Adults and 1 L/day for children
5Within each of these categories, the subgroup with the highest food exposure was given

Table 9. Drinking Water Levels of Concern for CHRONIC Exposure (using Food Exposure from DEEM)

Population Category5	Chronic RfD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure1 (mg/kg/day)	DWLOC 2,3, (µg/L)
U.S. Population (48 states)	0.03	0.0037	0.026	910
Females (13+ years, nursing)	0.03	0.0057	0.024	720
Infants/Children	0.03	0.011	0.019	190

1Maximum Water Exposure (Chronic) (mg/kg/day) = Chronic RfD (mg/kg/day) - Food Exposure (mg/kg/day)
2 DWLOC(µg/L) = Max. water exposure (mg/kg/day) * body wt (kg) ÷ [(10-3 mg/µg) * water consumed daily (L/day)].
3Default body weights are70 kg for the General U.S. Population, 60 kg for Females, and 10 kg for Infants/Children
4 HED Default Daily Drinking Rates are 2 L/day for Adults and 1 L/day for children
5Within each of these categories, the subgroup with the highest food exposure was given

The estimated average and peak concentrations of tebuconazole in surface water (after dividing the GENEEC model numbers by three) are less than HED's levels of concern for tebuconazole in drinking water as a contribution to chronic and acute aggregate exposure. Therefore, taking into account the present uses and uses proposed in this Section 3 and the fact that GENEEC can substantially overestimate (by up to 3X) true pesticide concentrations in drinking water, HED concludes with reasonable certainty that residues of tebuconazole in drinking water (when considered along with other sources of chronic exposure for which HED has reliable data) would not result in unacceptable levels of chronic (non-cancer and cancer) and acute aggregate human health risk estimates at this time.

HED bases this determination on a comparison of estimated average concentrations of tebuconazole in surface water to back-calculated "levels of concern" for tebuconazole in drinking water. These levels of concern in drinking water were determined after HED has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in these actions. The estimates of tebuconazole in surface water are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of tebuconazole in drinking water as a part of the chronic (non-cancer and cancer) and acute aggregate risk assessment process.

5) Aggregate Risk

a) Acute Aggregate Risk

For acute dietary exposure, the FQPA Safety Factor Committee determined that the 10X safety factor is applicable to the subpopulations females (13+ years), as well as infants and children because the effects seen were developmental and are presumed to occur following

"acute" exposures.

Application of the 10X safety factor for enhanced susceptibility of infants and children to the Acute RfD of 0.1 mg/kg/day results in an acceptable acute dietary exposure of 10% or less of the Acute RfD for the subpopulations females (13+ years), infants and children.

The acute dietary (food only) risk assessment used the Monte Carlo analysis submitted in conjunction with PP#5F4577 (MRID Nos. 445646-01, dated: 5/20/98). A detailed review of the analysis was performed by HED (8/21/98 memo, W. Wassel, DP Barcode 248264). The assumptions of the Monte Carlo analysis were summarized previously. This analysis should be considered highly refined.

The acute DWLOC for the population subgroup Females (13+ years) is 200 µg/L. This value is substantially higher than the surface water acute EEC (14 µg/L in surface water; GENEEC peak value) and the ground water EEC (0.3 µg/L, SCI-GROW value) for tebuconazole. The acute DWLOC for infants/chlidren is 14 µg/L. This value exceeds the GENEEC peak value (after dividing by three) and ground water EEC. Despite the potential for exposure to tebuconazole in drinking water, HED does not expect the acute aggregate exposure to exceed 10% of the Acute RfD (highest allowable value for this active ingredient). HED concludes that there is a reasonable certainty that no harm will result to Females (13+ years) and infants/children from acute aggregate exposure to tebuconazole residues.

b) Chronic (Non-cancer) Aggregate Risk.

Using the conservative TMRC exposure assumptions, and taking into account the completeness and reliability of the toxicity data, HED has estimated that chronic dietary exposure to tebuconazole from food only will utilize 12% of the chronic RfD for the population subgroup U.S. Population with the maximum utilized being 41% for children (1-6 years old). This is a conservative risk estimate for reasons described above. HED generally has no concern for exposures below 100 percent of the RfD (when the FQPA safety factor has been removed) because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health.

The chronic DWLOC for the U.S. Population (48 states) is 910 µg/L and for infants/children is 190 µg/L. These values are substantially higher than the surface water chronic EEC (10 µg/L, GENEEC 56 day average) and the ground water EEC (0.3 µg/L, SCI-GROW value) for tebuconazole. Despite the potential for exposure to tebuconazole in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the Chronic RfD. Tebuconazole registered residential uses include the formulation of wood-based composite products, wood products for in-ground contact, plastics, exterior paints, glues and adhesives. Under current HED guidelines, the registered non-dietary uses do not constitute a chronic exposure scenario. HED concludes that there is a

reasonable certainty that no harm will result from chronic (non-cancer) aggregate exposure to tebuconazole residues.

c) Short- and Intermediate-Term Aggregate Risk.

Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water (considered to be a background exposure level) plus indoor and outdoor residential uses. Residential exposure to tebuconazole is not expected via oral or inhalation routes, but dermal exposure could occur. No short- or intermediate-term dermal endpoints were identified. Thus, short- and/or intermediate-term risk assessments are not required.

d) Food Quality Protection Act Considerations

(i) Cumulative Risk

Tebuconazole is a member of the triazole class of systemic fungicides (*The Pesticide Book*, 4th ed., 1994). Other triazoles include bitertanol, cyproconazole, diclobutrazole, difenoconazole, diniconazole, fenbuconazole, flusilazole, hexaconazole, myclobutanil, penconazole, propiconazole, tetraconazole, triadimefon, and triadimenol.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides

that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

HED does not have, at this time, available data to determine whether tebuconazole has a common mechanism of toxicity with other substances or the means to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, HED has not assumed that tebuconazole has a common mechanism of toxicity with other substances.

(ii) Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

IV. ACTIONS REQUIRED BY REGISTRANTS

A. Additional Generic Data Requirements

1. Toxicology Studies

The HIARC recommended that the registrant be required to perform and submit to the Agency a developmental neurotoxicity study (Guideline 83-6, OPPTS Guideline 870.6300). The lack of this study should not preclude establishment of the requested tolerances. The submission of this study, however, should be made a condition of the establishment of the tolerances.

2. Residue Chemistry

A revised Section F specifying the tolerances in Table 1 of the Executive Summary is needed.

cc: RAB2 File, S.Weiss, E. Budd, PP#6F4669, PP#5F4577