

8/20/96

tebuconazole

MEMORANDUM

SUBJECT: PP#6F04669 Tebuconazole (Elite 45 DF, EPA Reg. No. 3125-388) in/on Grapes. **Evaluation of Analytical Methodology and Residue Data.**

MRID Nos. 439231-01 & -02; Chemical No. 128997; Case: 287342
 CBTS No. 17286; DP Barcode: D227017.

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Executive Summary of Residue Chemistry Deficiencies:

* Revised Section B.

Summary/Background:

Bayer Corporation requests the establishment of a tolerance 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. Tolerances are established under 40 CFR §180.474 for residues of the fungicide tebuconazole in or on bananas at 0.05 ppm, peanuts at 0.1 ppm and peanut hulls at 4.0 ppm.

Tebuconazole is not a FIFRA '88 reregistration active ingredient.

The chemical structure of tebuconazole is as follows:

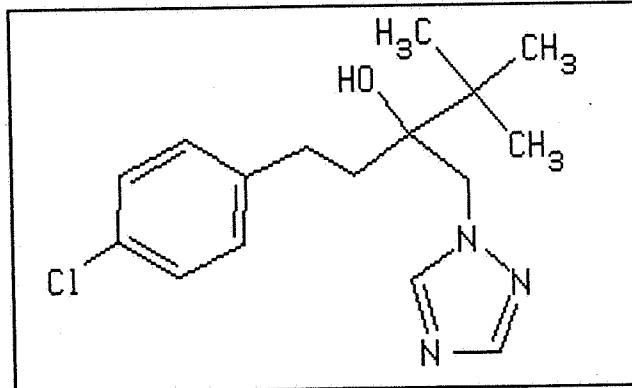


Figure 1 Tebuconazole

Conclusions:

1a. Product chemistry data were not submitted in conjunction with the subject petition. The petitioner has previously submitted product chemistry for technical grade tebuconazole in conjunction with PP#9F3724 and PP#3F4167. CBTS reiterates from our previous reviews that the product chemistry data requirements for technical grade tebuconazole have been satisfied.

1b. Based upon a Confidential Statement of Formula (CSF) dated 1/10/92, the technical product (EPA Reg. No. 3125-383) contains 96% tebuconazole. CBTS does not expect detectable residues (>0.01 ppm) of the impurities of the technical product in/on grapes when it is formulated into ELITE 45 DF Foliar Fungicide and used as proposed in the subject petition.

2. CBTS concludes the proposed directions for use of ELITE 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) on grapes are not adequate. The following deficiency should be addressed: under the "General Directions" section of the label, the growth stage of the vines at the final application should be specified (ie. 5° Brix stage or until veraison (berry coloring) is complete).

3. The metabolism of tebuconazole in/on grapes, wheat, and peanuts has been discussed in our reviews of PP#9G3817 and PP#9F3724. CBTS has previously concluded the nature of the residue in grapes is adequately understood. As metabolite residues were not identified at significant quantities in the previously submitted grape metabolism study and the HED Metabolism Committee has previously determined the residue of concern in peanuts to be tebuconazole, CBTS can conclude the residue of concern in grapes is tebuconazole.

4. The nature of the residue in rotational crops is not of concern for the subject petition as grapes are not normally rotated.

5. The nature and magnitude of the residue in animals is not of concern for the subject petition as there are no livestock feedstuffs associated with grapes (Table 1, 7/31/96).

6a. 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.

6b. An enforcement method (Bayer Method 101341, GLC/NPD) for the determination of residues of tebuconazole in crops has been sent to the FDA for inclusion in PAM II. This method has not yet appeared in PAM II, but is available in the interim from PRPRB/FOD. A slightly modified version of this method was utilized for analysis of field samples in the submitted magnitude of residue studies. CBTS concludes adequate methodology for enforcement of the proposed tolerances in/on grapes are available.

6c. CBTS concludes Bayer Method 101341, as modified, has been adequately validated for collection of residue data for tebuconazole in/on grapes and grape processed products.

7. Based upon the available storage stability data, CBTS would not expect residues of tebuconazole in/on grapes and grape processed products to degrade prior to analysis in the submitted magnitude of residue studies.

8a. The petitioner has submitted results from a total of 15 field trials from the Regions I (3 trials), II (1 trial), V (2 trials), XI (3 trials), and X (6 trials). The submitted field trials were initiated prior to the issuance of "EPA Guidance on Number and Location of Domestic Crop Field Trials For Establishment of Pesticide Residue Tolerances" (June 1994). CBTS concludes the geographic representation of the major grape growing regions of the U.S. in the submitted field trials is adequate.

8b. CBTS 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.

8c. The highest tebuconazole residue level in grapes at a 13 day PHI in the submitted studies was 3.95 ppm for the St. Helena, CA study. However, at a 19 day PHI residue levels increased to 4.63 ppm. This result is not considered unusual, as similar results were noted in other field trials. For tolerance setting purposes, CBTS will consider the highest residue level to be 4.63 ppm for tebuconazole in/on grapes.

9a. CBTS concludes an adequate grape processing study has been submitted in conjunction with the subject petition. The study shows that residues of tebuconazole do not concentrate in grape juice upon processing.

9b. CBTS concludes food additive tolerances for residues of tebuconazole in/on raisins are not required for the proposed use.

10. The International Tolerance Status Sheet is attached. 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 CBTS 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. CBTS 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.

Recommendations:

Toxicological considerations permitting and provided a revised Section B is submitted (see Conclusion 2, above), CBTS can recommend for the establishment of the proposed tolerance for residues of tebuconazole in or on grapes at 5.0 ppm.

A DRES run can be initiated using the proposed tolerance level of 5.0 ppm for residues of tebuconazole in/on grapes. Concentration of residues into grape juice and/or raisins is not expected.

Detailed Considerations:

Manufacture and Formulation:

Product chemistry data were not submitted in conjunction with the subject petition. 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). CBTS reiterates from our previous reviews that the product chemistry data requirements for technical grade tebuconazole have been satisfied. Based upon a Confidential Statement of Formula (CSF) dated 1/10/92, the technical product (EPA Reg. No. 3125-383) contains 96% tebuconazole. CBTS does not expect detectable residues (>0.01 ppm) of the impurities of the technical product in/on grapes when it is formulated into ELITE 45 DF Foliar Fungicide and used as proposed in the subject petition.

ELITE 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) has been proposed for use on grapes in conjunction with the subject petition. This product contains 45% by weight the active ingredient (ai) tebuconazole [α -[2-(4-chlorophenyl)ethyl]- α -(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol].

Proposed 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.

CBTS Comments/ Conclusions:

CBTS concludes the proposed directions for use of ELITE 45 DF Foliar Fungicide (EPA Reg. No. 3125-388) on grapes are not adequate. The following deficiency should be addressed: under the "General Directions" section of the label, the growth stage of the vines at the final application should be specified (ie. 5° Brix stage or until veraison (berry coloring) is complete).

Nature of the Residue - Plants:

Plant metabolism data were not submitted in conjunction with the subject petition. The metabolism of tebuconazole in/on grapes, wheat, and peanuts has been discussed in our reviews of PP#9G3817 (C. Olinger, 6/8/90, DEB No. 6022) and PP#9F3724 (G. Otakie, 5/9/91 and 2/16/93, CB No. 5667 and D174886, respectively). CBTS has previously concluded that the nature of the residue in grapes is adequately understood.

In the previously submitted grape metabolism study (PP#9G3817, C. Olinger, 6/8/90, DEB No. 6022), a single application of ¹⁴C-tebuconazole was made to grape vines at 0.25 lbs ai/A. This application rate represents 2.2x the single application rate or 0.28x the maximum seasonal rate. Grapes were harvested 0, 3, 7, 14, 21 and 28 days following application. In the 14, 21 and 28 day PHI samples, approximately 92 to 95% of the total radioactive residue (TRR) were identified as tebuconazole. A majority of the parent residues (85 to 89% of the TRR) were identified as surface residues with a small portion identified in a methanol extract of the homogenized fruit. Metabolite residues at significant quantities (>10% TRR) were not identified in these samples.

The metabolism of tebuconazole in/on peanuts was the subject of a meeting of the HED Metabolism Committee on 12/15/92 (see our memo of 12/17/92, G. Otakie). In this meeting, it was concluded that the tolerance expression for tebuconazole on peanuts should include the parent compound only.

CBTS Comments/Conclusions:

CBTS concludes the nature of the residue in grapes is adequately understood. As metabolite residues were not present in the previously submitted grape metabolism study and the HED Metabolism Committee has previously determined the residue of concern in peanuts to be tebuconazole, CBTS can conclude the residue of concern in grapes is tebuconazole.

Nature of the Residue - Rotational Crops:

The nature of the residue in rotational crops is not of concern for the subject petition as grapes are not normally rotated.

Nature and Magnitude of the Residue - Animals:

The nature and magnitude of the residue in animals is not of concern for the subject petition as there are no livestock feedstuffs associated with grapes (Table 1, 7/31/96).

Analytical Methods - Enforcement and Data Collection:**Enforcement:**

The petitioner has previously submitted data concerning the recovery of tebuconazole and its t-butylhydroxy metabolite by the FDA Multiresidue Methods of PAM I (see our memo of 2/16/93, G. Otakie, PP#9F3724/9F3818, D170444). Residues of tebuconazole and its t-butylhydroxy metabolite are not recoverable by these methods.

An enforcement method (Bayer Method 101341, GLC/NPD) for the determination of residues of tebuconazole in crops has been sent to the FDA for inclusion in PAM II (see our correspondence of 9/6/94, from G. Otakie, EPA, to A. Marcotte, FDA, PP#9F3724, D207313). This method has not yet appeared in PAM II, but is available in the interim from PRPRB/FOD. A modified version of this method (described below) was utilized for analysis of field samples in the submitted magnitude of residue studies.

CBTS Comments/Conclusions:

CBTS concludes adequate methodology for enforcement of the proposed tolerances in/on grapes are available.

Data Collection:

The analytical portions of the submitted field trial studies were performed by Bayer Corporation at their Stilwell, KS facility. The analytical portion of the processing study was performed at ABC Laboratories of Columbia, MO. The analytical method utilized for the determination of residue levels in the submitted studies was a modified version of the method entitled: "Gas Chromatographic Method for Determination of Residues of Tebuconazole in Crops, Processed Products, Soil and Water" by R.G. Minor, Bayer Ag Div Report No. 101341 (MRID No. 429098-01). This has been submitted to the FDA for inclusion in PAM II. The method modification omitted the GPC cleanup specified in the original method.

Briefly, residues were extracted from grapes by blending the sample material in acetone. Grape processed products (raisins, raisin waste and grape pomace) were extracted by blending with acetone/water (3:1). The filtered extract was partitioned with methylene chloride. Residues were extracted from grape juice by partitioning directly with methylene

chloride. The methylene chloride extracts were retained and cleaned by solid phase extraction utilizing silica gel followed by C-18. Residue levels of tebuconazole were determined by gas chromatographic analysis utilizing a nitrogen-phosphorus detector and a packed glass column.

The method was validated to a limit of quantitation (LOQ) of 0.01 ppm for residues of tebuconazole in/on grapes and to an LOQ of 0.08 ppm for grape processed products and grape juice. The method was validated concurrent with the analysis of treated samples. The results of fortification recovery samples for tebuconazole from grapes and grape processed products are summarized in Table 1.

Table 1. Recovery of Tebuconazole from Grapes and Grape Process Products.

Matrix	Fort. Levels ¹ (ppm)	Ave. Rec. ± Std. Dev. ²	Rec. Range ³
Grapes	0.01 (2)	91.0 ± 12.6%	70 to 112%
	0.02 (1)		
	0.05 (1)		
	0.10 (7)		
	10.0 (1)		
Raisin	0.08 (1)	110 ± 3.5%	107 to 112%
	0.32 (1)		
Raisin Waste	0.08 (1)	102 ± 8.9%	92 to 109%
	0.32 (1)		
	10.0 (1)		
Wet Pomace	0.08 (1)	101 ± 5.3%	95 to 105%
	0.32 (1)		
	10.0 (1)		
Dry Pomace	0.08 (1)	98.3 ± 11.0%	91 to 111%
	0.32 (1)		
	10.0 (1)		
Juice	0.08 (1)	92.5 ± 2.1%	91 to 94%
	0.32 (1)		

¹ Number in parentheses indicates the number of fortifications at that level.

² Average Recovery ± Standard Deviation (C_{-1}). The fortification recovery results were corrected for apparent residues in the control samples.

³ Recovery Range.

CBTS Conclusions/Comments:

CBTS concludes Bayer Method 101341 has been adequately validated for collection of residue data for tebuconazole in/on grapes and grape processed products.

Storage Stability:

Data pertaining to the stability of tebuconazole residues in or on grapes and grape processed products were not submitted in conjunction with the subject petition. Previously, 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). Samples from the submitted field trials were analyzed within ~10 months (315 days) of harvest, while samples from the processing study were analyzed within ~5 months (148 days) of harvest.

CBTS Comments/Conclusions:

Based upon the available storage stability data, CBTS would not expect residues of tebuconazole in/on grapes and grape processed products to degrade prior to analysis in the submitted magnitude of residue studies.

Magnitude of Residue - Crop Field Trials: (MRID No. 439231-01)

Field residue studies were conducted in NY, NC, MI, CA (3) and WA during 1991 in order to determine the residue levels of tebuconazole resulting from the proposed use of the product on grapes. The field trials included the following grape varieties: Chardonay, Zinfandel, Catawba, Concord, Thompson Seedless, and Muscadine. Each trial consisted of two plots (one treated and one untreated). The treated plots received eight applications of ELITE 45 DF at 1.8 oz ai/A/application (0.1125 lbs ai/A) for a total seasonal application rate of 14.4 oz ai/A (0.9 lbs ai/A). The interval between applications ranged from 5 to 10 days. Applications were made in 50 to 150 gallons per acre using an airblast sprayer. Treated grapes were harvested at intervals of 7 (± 1), 14 (± 1), and 21 (± 4) days following the final application. The 14 day PHI samples represent the proposed use. Samples were stored on ice immediately following harvest and maintained frozen (-20°C) when not actively in use. The grape samples were analyzed according to the method described above. Residue levels of tebuconazole were below the method quantification limit (0.01 ppm) in all untreated samples. The results of the analysis of treated samples are summarized in Table 2.

Table 2. Residue Levels of Tebuconazole in/on Grapes Following Eight Applications at 0.11 lbs ai/A.

Site (Region)	Preharvest Interval (days)	Residue Levels ¹ (ppm)
Phelps, NY (I)	7	0.37
	14	0.27
	21	0.18
Garner, NC (II)	7	0.85
	14	0.94
	21	0.74
Fennville, MI (V)	7	0.51
	14	0.56
	21	0.21
St. Helena, CA (X)	6	2.85
	13	3.95
	19	4.63
Temecula, CA (X)	7	1.72
	14	1.77
	25	1.67
Fresno, CA (X)	7	0.20
	14	0.20
	21	0.15
Yakima, WA (XI)	7	0.84
	14	0.67
	21	0.55

¹ Residue levels are not corrected for concurrent fortification recovery.

Additional residue data for tebuconazole in/on grapes were previously submitted in conjunction with PP#9G3817 (MRID Nos. 409959-34 and -35, see our review of 6/8/90, C.L. Olinger, DEB No. 6022). This additional data consists of eight residue field trials conducted during 1987 in NY (2), OR, WA, CA (3), and MI. In these trials tebuconazole was applied eight times at 0.11 lbs ai/A (45 DF or 1.2 EC formulation) for a total seasonal application rate of 0.9 lbs ai/A. These trials mimic the

proposed use of the subject petition. Samples were analyzed within eight months of harvest and stored frozen when not actively in use. Samples were analyzed according to Bayer Method 94295, this method is a earlier version of Bayer Method 101341, described above. Residue levels of tebuconazole were below the method quantification limit (0.01 ppm) in all untreated samples. The results of these trials are summarized in Table 3.

Table 3. Residue Levels of Tebuconazole in/on Grapes Following Eight Applications at 0.11 lbs ai/A.

Site (Region)	PHI	Application Interval (days)	Residue Levels (ppm)	
			45 DF Formulation	1.2 EC Formulation
NY-1 (I)	14	9-18	0.43	0.28
	21		0.28	0.20
NY-2 (I)	14	9-18	0.29	0.25
	21		0.46	0.33
OR (XI)	14	14	0.37	0.72
	21		0.27	0.37
WA (XI)	14	12-21	0.56	0.84
	21		1.0	0.73
CA-1 (X)	14	13-15	1.5	0.98
	21		0.56	0.60
CA-2 (X)	14	14-15	1.2	1.5
	21		1.4	0.93
CA-3 (X)	14	8-26	0.39	0.99
	21		0.41	0.81
MI (V)	14	13-19	0.10	0.07
	21		0.07	0.12

CBTS Comments/Conclusions:

The petitioner has submitted results from a total of 15 field trials from the Regions I (3 trials), II (1 trial), V (2 trials), XI (3 trials), and X (6 trials). The submitted field trials were initiated prior to the issuance of "EPA Guidance on Number and Location of Domestic Crop Field Trials For Establishment of Pesticide Residue Tolerances" (June 1994). CBTS concludes the geographic representation of the major grape growing regions of the U.S. in the submitted field trials is adequate.

CBTS 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.

The highest tebuconazole residue level in grapes at a 13 day PHI in the submitted studies was 3.95 ppm for the St. Helena, CA study. However, at a 19 day PHI residue levels increased to 4.63 ppm. This result is not considered unusual, as similar results were noted in other field trials. For tolerance setting purposes, CBTS will consider the highest residue level to be 4.63 ppm for tebuconazole in/on grapes.

Magnitude of Residue - Processed Commodities: (MRID No. 439231-02)

In order to obtain grape samples containing detectable residues of tebuconazole for a processing study, a field trial was performed in Fresno, California during 1991. In this trial, grapes were treated four times at a rate of 3.6 oz ai/A/application (0.225 lbs ai/A) for a seasonal application rate of 0.9 lbs ai/A). Applications were made on a 7 day spray interval. Mature grape samples (Thompson Seedless) were harvested on the day of the final application.

Samples were processed to raisins (sun-dried and oven-dried), wet and dry pomace, raisin waste (sun-dried and oven-dried), and juice utilizing procedures which were intended to simulate commercial grape processing practices. A complete description of the processing procedures were submitted. Sample processing were performed at The National Food Laboratory in Dublin, CA. Sample analyses were performed at ABC Laboratories of Columbia, MO. Upon processing, each commodity was transferred to frozen storage. All samples remained frozen except when actively in use. Samples were analyzed according to Bayer Method 101341, described above. Residue levels of tebuconazole were below the method LOQ for all untreated samples. The results of the analysis of treated samples are summarized in Table 4.

Table 4. Residues of Tebuconazole in Grape Processed Commodities.

Commodity	Residue Level ¹ (ppm)	Concentration Factor
Grapes	0.16	---
Sun-Dried Raisins	0.14	0.88
Sun-Dried Raisin Waste	0.64	4.0
Oven-Dried Raisins	0.21	1.3
Oven-Dried Raisin Waste	1.7	10.6
Wet Pomace	1.2	7.5
Dry Pomace	3.5	21.9
Juice	<0.08	<1.0

¹ Residue levels are not corrected for procedural recoveries.

CBTS Comments/Conclusions:

CBTS concludes an adequate grape processing study has been submitted in conjunction with the subject petition. The study shows that residues of tebuconazole do not concentrate in grape juice upon processing.

Raisins are considered a ready to eat food for tolerance setting purposes. In order to determine the need for Section 409 tolerances for residues in/on raisins, CBTS will average the concentration factors for the processing of grapes to raisins (oven-dried and sun dried). The average concentration factor is 1.1X. If we multiply the concentration factor by the highest residue level (4.63 ppm), a value of 5.09 ppm is obtained. This value is above the proposed tolerance limit of 5.0 ppm for residues of tebuconazole in/on grapes, but is within variability of the analytical method. CBTS concludes food additive tolerances for residues of tebuconazole in/on raisins are not required for the proposed use.

Attachment (1): 1. IRL Status Sheet

cc: WDWassell, RF, Circ., PP#6F4669, C. Welch/K. Scanlon (PM-21, RD, 7505C), F. Ives (CBTS).

RDI:TPTI: 08/06/96; RALoranger: 08/09/96; ETHaebere: 08/12/96.
7509C:CBTS:WDWassell:wdw:CM#2:Rm 804U:(703)305-6135:7/29/96.
Disk: WDW-7, File: Tebuconazole.1.

