2G4038

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

EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAY 14 1992

MEMORANDUM

SUBJECT: PP No. 2G4038/707-EUP-REL. Request for a Temporary Tolerance and Experimental Use Permit for Fenbuconazole on Pecans. Review of Residue Chemistry Data and Analytical Methodology. MRID Nos. 418750-36, -42, 418925-01, -02, -03. CBTS Nos. 9043, 9044. HED Project Nos. 2-0702, 2-0703. DP Barcode Nos. D171968, D171956.

FROM: Stephanie H. Willett, Chemist
Tolerance Petition Section II
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

THRU: Debra F. Edwards, Ph.D., Acting Branch Chief
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker/Dolphine Wilson, PM Team 22
Herbicide-Fungicide Branch
Registration Division (H7505C)

This review has been expedited at the request of RD. The requested due date is May 15, 1992 (see 4/24/92 memo of A. Lindsay).

Rohm and Haas is requesting the establishment of a temporary tolerance for fenbuconazole (alpha-2-(4-chlorophenyl)ethyl)-alpha-phenyl-1-H-1,2,4-triazole-1-propanenitrile) on pecans at 0.1 ppm in conjunction with an experimental use. Fenbuconazole (aka fenethanil, RH-7592) is a new fungicide and no permanent tolerances are established. A temporary tolerance of 1.0 ppm on stonefruit was established as a result of PP No. 9G3746. CBRS (then DEB) recommended against a temporary tolerance on almonds (see PP No. 9G3801/707-EUP-REU, 1/3/90 memo of F. Suhre).

Conclusions

1. CBTS concludes that the product chemistry data previously reviewed for fenbuconazole are adequate for the purposes of the proposed temporary tolerance on pecans (see F. Suhre memo dated 11/15/89). The additional product chemistry data

referenced by the petitioner will be reviewed in conjunction with the pending permanent tolerance petitions.

2. The proposed use has been adequately described.

3. Based on the peach metabolism study data, CBTS can consider the nature of the residue in plants to be adequately understood for the purposes of a temporary tolerance on pecans. The residue to be regulated is the parent compound.

   The wheat metabolism study referenced by the petitioner will be reviewed in conjunction with the pending permanent tolerance petitions on stonefruit and pecans. However, the petitioner is reminded that CBTS requires metabolism studies on three dissimilar crops which show similar metabolic pathways before the nature of the residue in <u>plants</u> is considered to be adequately understood. Therefore, we will not translate data from peaches or wheat to pecans for the purposes of establishing a permanent tolerance on pecans. A third plant metabolism study will be needed. CBTS will confer with TOX to determine which metabolites will need to be regulated.

   The metabolism of fenbuconazole in animals is not an issue related to this tolerance request.

4. Method No. 34-91-14 appears to be adequate for residue data collection and enforcement of a 0.1 ppm temporary tolerance on pecans based on the results of the independent lab validation. This method will also be validated by EPA since the extraction and cleanup procedures differ significantly from those of the stonefruit methodology, and method 34-91-14 determines additional metabolites. Also, based on the petitioner's recovery data and chromatograms, it is questionable whether or not the method can quantify residues as low as 0.01 ppm as the claims (see conclusion 5).

5. **CBTS concludes that the residue data and the supporting storage stability data on stonefruit are adequate <u>only</u> for the purposes of establishing a temporary tolerance for fenbuconazole (RH-7592) on pecans. The proposed tolerance of 0.1 ppm is adequate to cover probable residue levels resulting from the proposed experimental use. Although the actual residue levels reported are not considered reliable, the data and supporting information indicate that residues in pecans are below 0.1 pm.**

   Additional storage stability data will be needed on pecans prior to the establishment of a permanent tolerance since critical parts of the study on almond nutmeat were conducted by Craven Labs, upon whose data the Agency will not rely until issues surrounding the validity of such data are resolved.

2

6. No animal feed items are derived from pecans (note feeding and grazing restrictions). Therefore the magnitude of the residue in animal commodities is not an issue related to this request for an EUP and temporary tolerance.

Recommendations

CBTS has no objection to granting an EUP for use of fenbuconazole on pecans. We recommend for the establishment of a temporary tolerance of 0.1 ppm.

Detailed Considerations

Product Chemistry

The petitioner has referenced product chemistry data submitted in support of previously requested temporary tolerances (9G3746, 9G3801) and the pending permanent tolerances on stonefruit and pecans (1F3989, 1F3995).

Information on the manufacture of technical grade fenbuconazole and the RH-7592 experimental formulation was previously reviewed in the 11/15/89 memo of F. Suhre. The manufacture of the TGAI and the end use product RH-7592 2F was considered to be adequately described for the purpose of the temporary tolerance on stone fruit. No residue problems were anticipated from the probable impurities in the TGAI.

Likewise, for the purposes of establishing a temporary tolerance on pecans, CBTS can consider the product chemistry data already reviewed to be adequate. The additional product chemistry data as required in the review in the 1/3/90 memo of F. Suhre (9G3801) will be reviewed in conjunction with the pending permanent tolerances.

Proposed Use

Experimental formulation RH-7592 2F is to be used to control downy spot, leaf scorch, powdery mildew and scab. The label directions specify an application rate of 6 to 8 fl. oz./A (0.09 to 0.125 lb ai/A), with application to begin at bud break and continue at 10 to 14 day intervals through pollination. Application at 14 to 21 day intervals through the cover sprays is specified. Not more than 2 qts RH-7592 2F/A/yr (1 lb ai/A/yr) is to be applied, using ground equipment only and a minimum spray volume of 50 gal/A. A minimum PHI of 28 days is specified. Grazing livestock in treated areas and/or feeding cover crops grown in treated areas to livestock is prohibited.

The petitioner intends to conduct 40 trials in Alabama (6), Georgia (15), Louisiana (6), Mississippi (4), Oklahoma (4) and Texas (4). A total of 200 acres will be treated, with a maximum of 200 lb active ingredient applied in one year. The EUP and temporary tolerance are requested for a two year period.

The proposed use has been adequately described.

Nature of the Residue

The petitioner has referenced a peach metabolism study submitted in support of the temporary tolerance on stonefruit (9G3746), and a wheat metabolism study submitted in support of the pending permanent tolerances on stonefruit and pecans (1F3989, 1F3995).

The peach metabolism study was reviewed in detail in the 11/15/89 memo of F. Suhre. To briefly summarize, two peach trees were treated individually with ^{14}C triazole labeled fenbuconazole, and ^{14}C-phenyl labeled fenbuconazole. Each tree received five applications in intervals of 20 to 25 days, with the final treatment given at 22 days prior to harvest. The total amount of radioactive pesticide applied was equivalent to 0.89 to 0.99 lb ai/A. Total radioactive residues were reported as follows:

TABLE 1. Uptake/Distribution and Decline in ^{14}C-Fenbuconazole Residues

	TRR (ppm equivalents RH-7592)			
	phenyl-label		triazole label	
PHI	Leaves	Fruit	Leaves	Fruit
0	9.9	0.44	3.8	0.37
7	5.3	0.06	3.5	0.11
14	5.3	0.08	3.1	0.11
22	3.0	0.08	0.8	0.12

The radioactivity in fruit (22 day PHI) was extracted using various solvents and extraction schemes in order to identify the radioactive residues. The chloroform and water extractable activity (72.1 phenyl and 90% triazole of TRR) was identified as follows:

TABLE 2. Characterization of Extracted Radioactivity from ^{14}C Fenbuconazole Treated Peaches

Component*	Phenyl-label %TRR (ppm)	Triazole-label %TRR (ppm)
RH-7592 (parent)	45.0 (0.036)	15.5 (0.020)
RH-9129	14.2 (0.011)	4.3 (0.006)
RH-3968	---	47.5 (0.062)
RH-4098	---	6.7 (0.009)
Unknowns (≤5)	4.9 (0.003)	12.3 (0.016)
Total	64.1 (0.11)	86.30 (0.11)

* See attachment 1 for structures

The temporary tolerance on stonefruit was established in terms of the parent only.

Based on the peach metabolism study data, CBTS can consider the nature of the residue in plants to be adequately understood for the purposes of a temporary tolerance on pecans. The residue to be regulated is the parent compound, RH-7592 (fenbuconazole).

The wheat metabolism study referenced by the petitioner will be reviewed in conjunction with the pending permanent tolerance petitions on stonefruit and pecans. However, the petitioner is reminded that CBTS requires metabolism studies on three dissimilar crops which show similar metabolic pathways before the nature of the residue in plants is considered to be adequately understood. Therefore, we will not translate data from peaches or wheat to pecans for the purposes of establishing a permanent tolerance on pecans. A third plant metabolism study will be needed. CBTS will confer with TOX to determine which metabolites will need to be regulated.

Since no animal feed items are derived from pecans, the metabolism of fenbuconazole in animals is not an issue related to this EUP and temporary tolerance request (grazing and feeding restrictions are stated on the proposed label).

5

Magnitude of the Residue

Analytical Methodology

The methodology used to determine residues of parent RH-7592 and three of its metabolites, RH-9129, RH-9130, and RH-6467 is described in Rohm and Haas technical report No. 34-91-14[1] (MRID No. 41892503). RH-9129 and RH-9130 are diastereomers. Residues are extracted from finely chopped pecans by Soxhlet extraction with hexane/2-propanol. The extract is concentrated to an oily residue. The residue is dissolved in toluene/acetone and cleaned up on Silica gel and then Florisil. The samples are further cleaned up with a C-18 solid phase extraction cartridge. RH-7592 and the metabolites are determined by capillary gas chromatography, equipped with a thermionic specific detector optimized for nitrogen selectivity. The limit of quantification as claimed by the petitioner is 0.01 ppm for all analytes. All components are detected in a single chromatographic run. The following recovery data were reported.

TABLE 3. Rohm and Haas Recovery Data for Method 34-91-14

Fort. Level (ppm)	% RH-7592 (Avg)	% RH-9130 (Avg)	% RH-9129 (Avg)	% RH-6467 (Avg)
0.04	70-122 (92)	67-114 (91)	57-99 (79)	61-111 (93)
0.02	84-108 (98)	75-113 (101)	(67-112) (91)	(71-134) (105)
0.01	49-104 (85)	60-123 (91)	51-122 (89)	48-153 (100)

The concentration of the parent and its three metabolites in treated samples was calculated by constructing a least squares linear regression curve, using external standards. Sample chromatograms of controls, standards and spikes were submitted. However none were of a 0.01 ppm standard. Chromatograms from recoveries at 0.01 are in the residue data report (MRID No.

[1]**Methods 34-91-02 and 34-91-14 are identical methods. See Rohm and Haas letter from Richard D. Costlow dated 5/12/92.**

6

41892502, TR 34A-91-09). Those from 0.01 ppm spikes indicate that quantitation at 0.01 ppm may not be reliable (see pages 151, 166, 197 and 221).

The analytical method was independently validated by Centre Analytical Labs (see TR 34-91-15, MRID No. 41892501). Samples of pecans were fortified with standards at 0.05 and 0.1 ppm. Recoveries ranged from 80 to 100%, 72 to 89%, 80 to 99% and 72 to 89% for RH-7592, RH-9129, RH-9130, and RH-6467, respectively.

Method No. 34S-88-20 was submitted with the request for a temporary tolerance on stonefruit. The method was successfully validated by EPA staff at 0.01, 0.1 and 1.0 ppm (see 11/15/90 memo of B. Puma ACS/BEAD). The stonefruit extraction and cleanup procedures differ significantly from those in method No. 34-91-14, and the stonefruit method was tested only on its abilities to determine the parent compound. In both methods, residues are determined by capillary chromatography, equipped with a thermionic detector (NPD detector used by EPA in lieu of thermionic detector).

Method No. 34-91-14 appears to be adequate for residue data collection and enforcement of a 0.1 ppm temporary tolerance on pecans based on the results of the independent lab validation. This method will also be validated by EPA since the extraction and cleanup procedures differ significantly from those of the stonefruit methodology, and method 34-91-14 determines additional metabolites. Also, based on the petitioner's recovery data and chromatograms, it is questionable whether or not the method can quantify residues as low as 0.01 ppm as the petitioner claims. Our recommendation for a temporary tolerance is not dependent upon completion of an EPA method validation.

Residue Data (MRID No. 41892502)

Experimental fungicide RH-7592 2L was applied to pecans in Texas, New Mexico, Georgia, and South Carolina (1 site/state) using handgun or airblast applicators. A total of 1 to 2.5 lb ai/A (1 to 2.5 maximum label rate) were applied in 8 to 10 equivalent applications in intervals of 13 to 30 days. Samples were harvested at 0, 7, 14 and 28 days after the final treatment, and shipped frozen or fresh to Rohm and Haas Research Laboratories in Spring House, PA for processing. Pecans from the New Mexico trial were green and immature and thus were dried in an oven at 100 °F for 4 hours to facilitate removal of the hulls and shells. All the nutmeats were then processed with dry ice, the dry ice allowed to sublime, and then stored frozen (-10 °C) until analyzed (92 to 137 days).

Sample analyses were performed at Rohm and Haas using analytical method the analytical methodology described above which determines parent RH-7592 and its metabolites RH-9129, RH-9130, and RH-6467.

Residues of RH-7592, RH-9129, RH-9130 and RH-6467 were reported as <0.01 ppm (claimed limit of quantification) in the 37 samples analyzed (0 to 28 day PHI, 1 to 2.5X). Chromatograms of controls, standards, spikes, and incurred residue samples were submitted. However, none were of a 0.01 standard. As stated previously, chromatograms from 0.01 ppm spikes indicate that quantitation at 0.01 ppm may not be reliable (see TR 34A-91-09, pages 151, 166, 197 and 221).

Storage Stability Data

The petitioner referenced storage stability data on stonefruit and almond nutmeat.

In the study on stonefruit (MRID No. 41875042), selected samples from residue trials were reanalyzed using method TR 34-90-47, which determines parent RH7592 and its lactone metabolites RH-9129 and RH-9130. This method is very similar to method 34S-88-20 which was used to initially determine residues of RH-7592. Method 34S-88-20 was successfully validated by EPA (see 11/15/90 memo of B. Puma, ACS/BEAD). Sixteen samples of cherries, plums and peaches containing measurable residues of RH-7592 were reanalyzed after 844 to 1025 days of storage at -15°C. The data indicate that there was no appreciable decline in residues during storage.

In the study on almond nutmeat (MRID No. 41875036), almond nutmeat was spiked at a level of 1.0 ppm with parent RH-7592 or RH-9129/ RH-9130 and stored in plastic jars at -15°C until analyzed after 0, 7, 14, 28, 60, 90 days, 6 months and 1 year in storage. Samples were analyzed using method TR-34-89-34 which determines RH-7592 and RH-9129/9130. Samples from 0, 7, 14, 28, 60, 90, days as well as the 6 month samples were analyzed by Craven Laboratories. The 1 year samples were analyzed at Rohm and Haas.

CBTS concludes that the residue data provided and the supporting storage stability data on stonefruit are adequate **only** for the purposes of establishing a temporary tolerance for RH-7592 on pecans. The proposed tolerance of 0.1 ppm is adequate to cover probable residue levels resulting from the proposed experimental use. Although the actual residue levels reported are not considered reliable, the data and supporting information indicate that residues in pecans are well below 0.1 pm.

Since the 0 day analyses were performed by Craven Laboratories, upon whose data the Agency will not rely until issues surrounding the validity of such data are resolved, the storage stability study on almond nutmeat will not be used to support a regulatory decision at this time. Additional storage stability data will be needed on pecans prior to the establishment of a permanent tolerance.

Meat, Milk, Poultry and Eggs

No animal feed items are derived from pecans (note feeding and grazing restrictions). Therefore the magnitude of the residue in animal commodities is not an issue related to this request for an EUP and temporary tolerance.

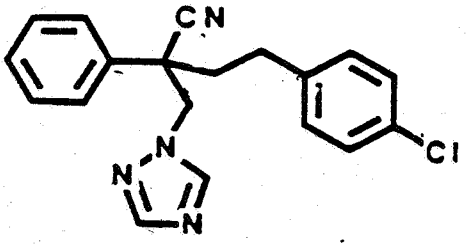
Attachment: Structures of - Fenbuconazole (RH-7592) and its Metabolites

cc: RF, 2G4038, S. Willett, E. Haeberer, Circ, PIB/FOD (C. Furlow)

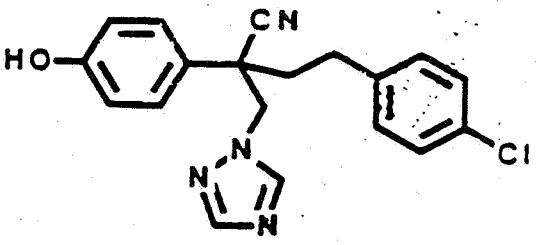
CM2:3056439:H7509C:SHWillett:shw-5/6/92
RDI: E. Haeberer, 5/5/92; R. Loranger, 5/8/92

Attachment 1

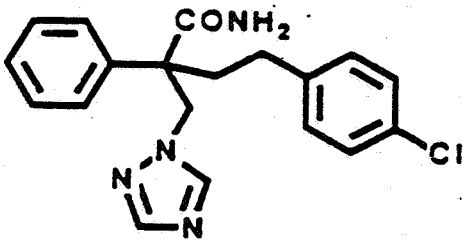
Structures of RH-7592 and Related Compounds



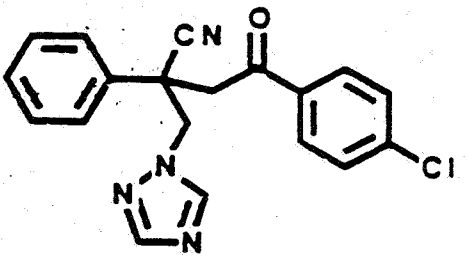
RH-7592



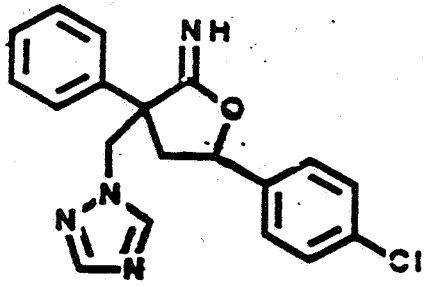
RH-1311



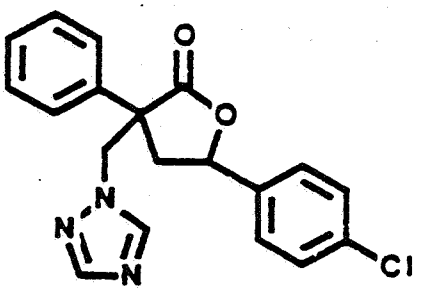
RH-0960



RH-6467



RH-6468



RH-6469

RH-9129 Diastereomer A
RH-9130 Diastereomer B

Metabolism of RH-7592