



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

JUN 20 1986

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4F3007: Tilt on Pecans - Amendment of
November 11, 1985 (Accession No. 074008;
RCB No. 280)

FROM: Alfred Smith, Chemist
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and

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Hazard Evaluation Division (TS-769C)

THRU: Charles L. Trichilo, Chief
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Ciba-Geigy has submitted an amendment for the fungicide Tilt (CGA-64250), 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole, and its metabolites containing the 2,4-dichlorobenzyl moiety in or on pecans at 0.1 ppm. The amendment is in response to deficiencies raised in the Residue Chemistry Branch review of May 15, 1984 (A. Smith). The conclusions containing the deficiencies are copied below.

- 1(a) The label statement on grazing should be changed to read, "Do not graze livestock in treated areas or cut treated cover crops for feed."
- 1(b) The application dosage should also be expressed as pounds active ingredient per 100 gallons of spray solution (consult EPA Pesticide Assessment Guidelines Subdivision O - Residue Chemistry).

- 2(b) Plant residues consist of the parent compound CGA-64250; free and conjugated metabolites containing the intact parent ring system (four hydroxylated derivatives of the parent compound, CGA-118241); free and conjugated components containing both the phenyl and triazole rings - CGA-91304, CGA-91305, and CGA-104284. The residues of the fruiting parts consist primarily of the aminoacid conjugate of the triazole ring, 1,2,4-triazole-1-alanine. (All components are determined by the analytical methods.) RCB defers to Toxicology Branch (TB) as to whether or not the residues containing the triazole moiety should be included in the tolerance expression for plant commodities.
- 2(c) Residues in animals (goats, rats, mice) consist of the parent compound CGA-64250 and metabolites containing the intact parent structure with hydroxy groups, carboxylic acid groups, or hydroxy acid groups on the alkyl side chain of the dioxolane ring (CGA-118244, CGA-118245, CGA-121676, alpha-hydroxy-carboxylic acid). These components appear free and as glucuronide and sulfate conjugates. Lesser quantities of residue components consist of the intact dichlorophenyl and triazole-ring structure, i.e., CGA-91304 and CGA-91305. These components may contain hydroxy and methoxy groups on the phenyl ring and appear free and as glucuronide and sulfate conjugates. Meat (liver) and milk contain, in addition to traces of the above components, triazole (CGA-71019), triazolealanine conjugate, and possibly the acetyl derivative of triazolealanine (about 50% of milk residues). In tissues the triazole ring is conjugated with aminoacids and possibly bound in protein linkages. Residues do not concentrate in the fat of meat or milk. Although no feed items are involved in this petition, RCB defers to TB as to whether or not the components containing the triazole moiety should be included in the tolerance expression for animal commodities to be considered in future proposed usages.
- 3(a) Two analytical methods are available for the determination of residue in crops. In one method residues of the parent compound CGA-64250 and metabolites containing 2 and 3 rings (free and

conjugated) are determined. The method's overall sensitivity is approximately 0.2 ppm. This level is greater than the proposed tolerance level of 0.1 ppm. The method is not sensitive enough to support the proposed tolerance. More important, however, if TB declares that all triazole residues must be included in the tolerance expression, then this procedure, as validated, should not be considered for regulatory purposes.

- 3(b) The second method determines residue components containing the triazole ring as the dibromomethyl derivative. However, untreated samples yielded triazole equivalent residues up to 2.6 ppm which seriously interfere with the determination of triazoles from treatment with CGA-64250. Therefore, the method is not adequate for the determination of residues of CGA-64250; improvements are needed. Analytical methods must be submitted which determine residues of CGA-64250 and its metabolites at levels which reflect the residues expected from the proposed use. The methods must be capable of distinguishing between residues due to treatment and background components. After the petitioner has resolved those deficiencies relating to the analytical methodology and as to what the appropriate tolerance level should be (see Conclusion 4 below), RCB will request an EPA method trial.
4. The residue data generated by the triazole procedure (AG-357) show, for example, pecan meats containing as much as 12 ppm total residues after six 1X applications and observance of 30-day intervals. As a result, we defer to TB for the toxicological significance of those residues containing the triazole moiety (1,2,4-triazole, etc.). If TB declares that triazole residues must be included in the tolerance expression, and the petitioner chooses to improve the triazole procedure, then the tolerance expression should be expressed as "... combined residues of the fungicide CGA-64250 ... and its metabolites determined as 1,2,4-triazole and expressed as the parent compound ... in or on pecans at ... ppm." At this time, it is not possible to reach a valid conclusion on an appropriate CGA-64250 (Tilt) tolerance for pecans.

The petitioner has submitted a revised Section B which contains the statement, "Do not graze livestock in treated areas or cut treated cover crops for feed." This statement is in accord with the change suggested in Conclusion 1(a). This deficiency is resolved.

In response to 1(b), Ciba-Geigy states that "... due to wide variation between the spray volume recommendations of the agricultural extension service in various pecan-producing States, it is impossible to be specific. For example, in Texas the dilute rate is 300 GPA with hydraulic sprayers, 75 to 300 GPA with air blast sprayers, and 50 GPA with mist blowers on large trees and the volumes are lower on medium and smaller trees; in Florida, the usual rates are 30 GPA with hydraulic sprayers and 7.5 to 30 GPA with air blast on large trees. Most growers elsewhere in the southeastern U.S. use 200 GPA or more." The petitioner considers the rate of chemical per acre to be the more critical use direction instead of spray volume. In order to account for tree size variation, the petitioner's use directions provide rates for trees over 30 feet tall and trees under 30 feet tall.

The petitioner's rationale for the dosage expression appears reasonable, and RCB accepts the explanation. The question in Conclusion 1(b) is resolved.

In response to Conclusion 3(a), the petitioner contends that the residue method's sensitivity is 0.1 ppm instead of the 0.2 ppm overall sensitivity estimated by RCB. The petitioner further states that since the nutmeat is the raw agricultural commodity, the sensitivity of the method should be based on data obtained with the nutmeats only instead of using data from both nutmeats and shells.

RCB agrees that the residue method's practical sensitivity is more appropriately determined with validation data for the nutmeats. The residue method (AG-356), "Determination of Total CGA-64250 Residues in Crops by Conversion to 2,4-Dichlorobenzoic Acid and Analysis by Gas Chromatography Mass Spectrometry," was used to obtain validation data for pecans. The method determines the parent compound CGA-64250 and its metabolites containing 2 and 3 rings (free and conjugated).

The untreated (control) nutmeat samples had no detectable (< 0.02 to < 0.05 ppm) CGA-64250 equivalent residues. Control nutmeat samples were fortified with CGA-64250 at levels of 0.05 to 2.0 ppm. Recoveries were 51 to 89 percent.

RCB concurs that the sensitivity of the residue method for nutmeats is approximately 0.1 ppm. Therefore, the residue method appears to be adequate for the determination of the parent compound CGA-64250 and its metabolites containing the 2,4-dichlorophenyl moiety.

A method trial with pecans has been requested in order to determine if the method is adequate for enforcement purposes. The foregoing discussion resolves the question on method sensitivity in Conclusion 3(a).

Questions in Conclusions 2(b), 2(c), 3(b), and 4 deal with those residue components containing only the triazole moiety. TB has not yet determined if such components are toxicologically significant and, therefore, should be included in the tolerance expression as part of the residue. As a result, questions raised in Conclusion 2(b), 2(c), 3(b) and 4 have not been resolved.

Method Trials

Method trials (MTO) are being requested for CGA-64250 in pecans (PP#4F3007), beef liver, milk, and eggs (PP#4F3074). The residue methods determine the parent compound (CGA-64250); the beta and gamma hydroxy derivative of the parent and their conjugates (CGA-118244 and CGA-118245); the olefin (CGA-104284); the ketone (CGA-91304) and the alkanol (CGA-91305) and their conjugates. (The structures are included in the accompanying figures of chemical names and structures.) These comprise the plant and animal residue components which have both the dichlorophenyl and triazole rings as part of their structures.

Because of the severity of the digestion conditions in the methods (approximately 70% nitric acid mixture under heat for 16 hours), the dichlorophenyl moiety of all components is expected to be converted to the benzoic acid derivative. This component is determined and expressed as the parent compound. Therefore, sample fortification with the parent compound, CGA-64250, adequately reflects the presence of all components mentioned.

If TB should determine that the triazole components are toxicologically significant, then the triazole components will be included in the tolerance expression. Once the deficiencies of the analytical methodology are resolved (see Conclusion 3(b)), a method trial may be requested to determine if an adequate method is available for enforcement purposes.

Conclusions

Questions raised in Conclusions 1(a), 1(b), and the method sensitivity in 3(a) have been resolved. However, the resolution of questions raised in Conclusions 2(b), 2(c), 3(b) and 4 are contingent upon toxicological considerations. TB has not yet completed its determination.

Recommendations

RCB recommends against the proposed tolerance. A favorable recommendation is contingent upon the results of the pecan method trial and TB response to questions on the triazole components (see Conclusions 2(b), 2(c), 3(a), 3(b), and 4).

cc: Reviewer, FDA, Circu., R.F., PMSD/ISB, TOX, RD, PP#4F3007
RDI, PVE, 6/5/86; RDS, 6/5/86

TILT CGA-64250 Reviews

The next 2 page(s) is/are not included in this copy of the TILT reviews.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients
 - ☐ Identity of product impurities
 - ☐ Description of the product manufacturing process
 - ☐ Description of product quality control procedures
 - ☐ Identity of the source of product ingredients
 - ☐ Sales or other commercial/financial information
 - ☐ A draft product label
 - ☐ The product confidential statement of formula
 - ☐ Information about a pending registration action
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