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SUBJECT: PP#1G2530. Tilt on rice and pecans

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CIBA-Geigy Chemical Corporation proposes the establishment of temporary tolerances for residues of the fungicide, 1-[[2-(2,4-dichlorophenyl)4-propyl-1,3-dioxolan-2-yl]methyl]-triazole (trade name Tilt) and its metabolites containing the 2,4,-dichlorobenzoic acid moiety in or on pecans at 0.1 ppm and in or on rice at 4 ppm.

The proposed experimental program involves the application of 824.4 lbs. a.i. of Tilt to 1638 acres of rice in five states, and the application of 720 lbs. a.i. to 1875 acres of pecans in twelve states.

Conclusions

1. The fate of Tilt in plants and animals has been adequately delineated for the purpose of the proposed temporary tolerance. Tilt, per se, and its metabolites containing the 2,4-dichlorobenzoic acid are the principal residues of concern.
2. Adequate methodology is available to enforce the proposed tolerances for residues on rice and pecans.
- 3a. The available residue data demonstrate that the proposed 4 ppm tolerance level for rice grain and the 0.1 ppm level for pecans will be adequate for the purpose of the proposed temporary tolerances.

- 3b. Residues in rice hulls will exceed the proposed 4 ppm tolerance for rice. A food additive tolerance to cover residues in rice hulls is needed; 15 ppm would be an appropriate level.
4. The available animal metabolism data indicate that secondary residues will result in meat, milk, poultry and eggs from the proposed use. Conventional cattle and poultry feeding studies are needed to determine the appropriate tolerance levels for meat, milk, poultry and eggs. Appropriate enforcement methodology and validation data for the meat, milk, poultry and egg tolerances will also be required.

#### Recommendations

1. We recommend against the establishment of the proposed tolerance for the reasons cited in Conclusions #3b and 4.
2. For a favorable recommendation the following will be required.
  - a) Analytical methodology to determine residues in meat, milk, poultry and eggs.
  - b) Validation data for this methodology demonstrating adequate recoveries and controls.
  - c) Conventional cattle and poultry feeding studies.
  - d) Proposal of appropriate tolerances for residues in meat, milk, poultry and eggs.
  - e) Proposal of a 15 ppm food additive tolerance to cover residues in rice hulls.
3. The following will be required for a future permanent tolerance:
  - a) Development of enforcement methodology that does not use the "processed" standard correction factor but instead uses methyl 2,4-dichlorobenzoate as a primary GLC standard.
  - b) Appropriate validation data for the modified enforcement methodology.
  - c) Additional residue data for both rice and pecans reflecting adequate geographical representation.

TILT CGA-64250 Reviews

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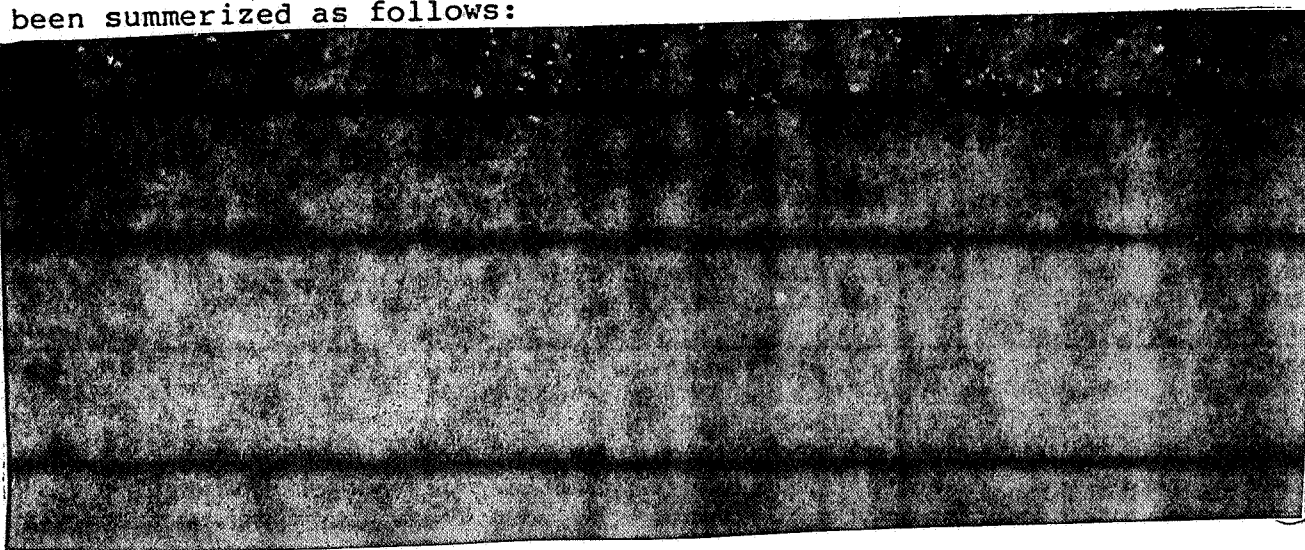
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We do not anticipate any residue problems from the impurities present in technical Tilt. The manufacturing process for Tilt has been summarized as follows:



#### Proposed Use

Tilt 3.6E is proposed for use to control of a variety of fungi on pecans and rice. Applications on pecans begin when young leaves are unfolding, and continue at 2-4 week intervals until shucksplit. Orchards with trees over 30 feet tall and those with trees less than 30 feet tall are to be treated at rates of up to 5.4 and 4 oz. per acre, respectively. A spray volume large enough to provide adequate coverage is required.

The use proposed for Tilt on rice recommends two applications of 4.5 oz. a.i. per acre, the first at booting and the second at heading. A 21 day preharvest interval is required and a restriction against the feeding or grazing of treated straw to livestock has been imposed.

#### Nature of the Residue

Plant Metabolism: Radiolabeled plant metabolism studies have been conducted in wheat, barley, and grapes. These studies demonstrate a similar metabolic pathway in these crops, which includes hydroxylation of the alkyl group on dioxolane ring, opening of the dioxolane ring and eventual cleavage of the carbon chain between the phenyl and triazole rings. Significant levels of metabolites containing the phenyl and triazole moieties have been detected in plant tissues.

Wheat was treated at early emergence with 0.112 lbs. of triazole-labeled Tilt per acre. Plants were sampled at 5 hours and at 11, 25 and 49 days after treatment.

The plants were divided into lower, middle and upper portions for analysis. Most of the activity remained in the upper portions of wheat (70% in the upper third, 19% in the middle section and 11% in the lowest section). Within 5 hours about 1/3 of the activity had penetrated into the plant. During the following 11 days little additional penetration occurred; however, surface residues did decline through volatilization.

The wheat plant fractions were washed with water and the activity washed off partitioned against methylene chloride and chromatographed on a silica gel thin layer plate. The plant material was extracted with methanol and then partitioned against water and methylene chloride. The unextractable activity was determined by combustion.

The recovered activity was characterized as Tilt, organo-soluble, polar soluble and non-extractable. The reported values for 5 hours, 11 days and 25 days are tabulated below:

Harvest Interval	Tilt	Organo-Soluble	Polar Soluble	Non-Extractable
5 hours	92.6	3.7	3.3	0.4
11 days	28.0	13.2	49.8	9.0
25 days	9.8	8.1	70.1	12.0

No parent compound was reported in the mature grain. Total activity reported in the mature grain was 0.39 ppm. The polar soluble activity is believed to be water soluble conjugates. The only experiments conducted to characterize the organo-soluble fraction indicated that most of the activity could be acetylated and that oxidation of the n-propyl group had occurred.

Both field grown and greenhouse peanuts were treated with either <sup>14</sup>C-triazole-ring-labeled Tilt or <sup>14</sup>C-phenyl-ring-labeled Tilt. The peanut plants were treated three times, twice at a rate equivalent to 0.125 lb a.i. per acre and once at a rate equal to 0.112 lb a.i. per acre. The mature peanuts were harvested 14 days after the last treatment.

Homogenized plant samples were extracted with several solvent systems, and partitioned between methylene chloride and aqueous methanol. The organo-soluble and polar-soluble metabolites were chromatographed in separate thin layer systems. The various fractions were then purified and analyzed by GC-MS, HPLC, GLC and NMR.

Approximately 90% of the total activity was solubilized. Enzymatic hydrolysis of the polar fraction released the following compounds:

alpha-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol (Metabolite A)

2-(2,4-dichlorophenyl)-alpha-methyl-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolane-4-ethanol (Metabolites B and B' stereo-isomers);

2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-propanol (Metabolite C and C' stereo-isomers).

At maturity the peanut plants contained approximately 11.7 ppm, 2.4 ppm and 14.3 ppm (equivalent Tilt) in the stalks, shells and peanuts, respectively. Essentially all of the activity found in mature peanuts was polar soluble. Peanut hulls contained 61% polar-soluble, 18% organo-soluble and 16% non-extractable. The activity found in the vines was 69% polar-soluble, 14% organo-soluble and 14% non-extractable. Approximately 55% of the polar soluble fractions were converted to Metabolites A, B, B', C and C' by the enzymatic hydrolysis. Approximately 7% of the activity in the mature peanut plants was identified as parent compound, while 40-50% of the remaining activity was shown to be Metabolites A, B, B', C or C' or water-soluble conjugates of these compounds. An additional 22% of the residue was shown to contain only the triazole ring. None of the activity in the mature peanut contained both the triazole and phenyl ring structures.

Grapes were treated four times at a rate equivalent to about 0.33 oz/100 gal of spray solution with either <sup>14</sup>C-ring-labeled or <sup>14</sup>C-triazole Tilt. The plants were sampled 30 and 63 days after treatment. Total activity levels in leaves, whole grapes, grape juice and pommace were determined. The activity was extracted from the various plant fractions with aqueous methanol and partitioned against methylene chloride. Total activity in the grapes never exceeded 0.05 ppm (equivalent to Tilt). The level of parent compound never exceeded 0.001 ppm in the grapes. The activity was characterized and or identified using thin layer chromatography, electrophoresis, hydrolysis, derivatization, reverse phase high pressure liquid chromatography and GC-MS. The results of these experiments demonstrate a similar metabolic pattern as that shown in peanuts.

In conclusion we can consider the fate of Tilt adequately delineated for the purpose of the proposed temporary tolerance, and that Tilt and its 2,4-dichlorobenzoic acid moiety containing metabolites are the residues of concern.

Animal Metabolism: A lactating goat was administered a mixture of cis and trans  $^{14}\text{C}$ -triazole-labeled Tilt at a level of 4.53 ppm for ten days. The animal was sacrificed 24 hours after the last dose. A total of 92% of the administered activity was recovered. Most of the activity was excreted via the urine 68.6% with 21% found in the feces. Approximately 0.18% was secreted in milk. Activity levels in milk plateaued on the third day of treatment at 0.13 ppm. Levels in tissues were less than 0.02 ppm except for kidney at 0.029 ppm and liver at 0.096 ppm. No parent compound was recovered from either excreta, milk or tissues.

Approximately 92% of the excreted activity was shown to contain both the phenyl and triazole ring structures. In fact at least 75% of the activity excreted via the urine had all three ring structures of the Tilt molecule. The excreted metabolites were chromatographed on two TLC systems and shown to be significantly polar.

Only 19% of the activity in milk and liver contained both the triazole and phenyl ring structures. Most of the activity (90%) in milk and 38% of the activity in liver could be converted to  $^{14}\text{C}$ -triazole. The major metabolite in milk is postulated to be a triazole conjugate of alanine and corresponds to approximately 50% of the recovered activity. No further investigations were conducted to identify the low levels of activity in the other tissues.

For the purpose of the proposed temporary tolerance we conclude that the fate of Tilt in animals has been adequately delineated.

#### Analytical Methods

The proposed analytical method for residues of Tilt, per se in crops is presented in Report #AG354. Residues of Tilt are extracted with aqueous methanol. The extract is then diluted with aqueous sodium chloride and partitioned against methylene chloride. The organic phase is evaporated to dryness and the residue redissolved in hexane and chromatographed on an alumina column. The appropriate elute is evaporated to dryness, redissolved in acetone and the Tilt residue determined by GLC using an alkali flame ionization detector.

A modified procedure which converts all of the Tilt residues to 2,4-dichlorobenzoic acid is proposed for enforcement of the tolerances. The available metabolism data indicate that the proposed total residue method should determine at least 85% of the total Tilt residues. This procedure includes hydrolysis of the residue acid by refluxing overnight with 12 N nitric and methylation of the hydrolyzate with diazomethane. A silica gel column is also used instead of the alumina column of AG 354. This procedure uses a "processed" standard to determine the levels of the methylated 2,4-dichlorobenzoic acid. Although we can consider such a method acceptable for the proposed temporary tolerances we do not consider such a procedure appropriate for the enforcement of permanent tolerances.

Recovery values for Tilt residues from rice grain ranged from 73 to 101% and averaged 86% control values were reported as less than 0.05 for rice grain. Recoveries from rice straw ranged from 77 to 95% and averaged 87%. The control rice straw values are reported as less than 0.10 ppm. Recovery of Tilt from pecans is only marginally acceptable, ranging from 56 to 67% and averaging 60%. Control values are reported as less than 0.05 ppm. For a future permanent tolerance additional recovery data showing adequate recoveries of Tilt from rice and pecans by a method that does not use a "processed" standard will be required. Also for a future permanent tolerance a sample of the derivatized 2,4-dichlorobenzoic acid for use as a primary standard should be made available.

#### Residue Data

Rice: Five residue studies were conducted on rice in four Southern states. Tilt was applied twice as a foliar spray at the maximum proposed rate of 4.5 oz. A.I. per acre. Applications were made at 13-15 day intervals and the grain was harvested 20-30 days after the last treatment. Samples of grain and straw as well as milling fractions were analyzed for residues of Tilt, per se, and its metabolites.

Residues in rice grain ranged from 0.37 to 3.9 ppm from the maximum proposed rate. There was little correlation between the preharvest intervals and residue levels. The highest level reported for the 2X applications was 1.2 ppm. We conclude that the proposed 4.0 ppm level will be adequate for the purpose of the temporary tolerance. Residue data for rice straw ranged as high as 10 ppm for the 1X applications. Additional residue data will be needed for a future permanent tolerance.

Milling fraction data were also developed from treated rice. Residues in the two unprocessed rice samples were 0.73 and 1.5 ppm. Residue level in their respective milling fractions (brown rice, white rice, bran and hulls) with the exception of the hulls were lower. Levels in the hulls were 1.5 to 3.3 times higher than the whole grain. It is our judgment that a 15 ppm food additive tolerance will be required for Tilt residues in rice hulls.

Pecans: Four residue studies in which pecans were treated 9 or 10 times at 1 or 2 times the maximum proposed rate were conducted in two states. The pecans were harvested 7 or 14 days after treatment and analyzed for total Tilt residues by methodology reportedly sensitive to 0.10 ppm. No detectable residues of Tilt were found in any pecan samples regardless of treatment rate or preharvest interval. We can conclude that the proposed 0.1 ppm temporary will be adequate to cover the residues that will result on pecans from the experimental program.

Storage stability tests were conducted with soybean grain and fodder fortified with Tilt. The study showed no significant decline in levels during frozen storage for the six months of the experiment.



Meat, Milk, Poultry and Eggs

Rice and rice milling products are the only animal feed items involved the proposed use. Rice may be fed to cattle at a rate 25% of the diet and to poultry at up to 40% of the diet. Therefore the proposed use could result in approximately 1 ppm and 1.6 ppm in the diet of cattle and poultry respectively.

No conventional feeding studies have been submitted. Nor have any tolerances for residues in meat, milk, poultry or eggs been proposed or any enforcement methodology been submitted. The submission of cattle and poultry feeding studies, appropriate analytical methodology, validation data and appropriate tolerance proposals for residues in meat, milk, poultry and eggs will be required for a favorable recommendation.

cc: Reading file  
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TS-769:Reviewer:JLWorthington:Rosa:EFB:Date:1/5/82  
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