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MEMORANDUM

Subject: **PP# 5E4590 - QUIZALOFOP-P ETHYL ESTER (ASSURE® II) ON PINEAPPLES.** Review of Magnitude of the Residue Data and Residue Analytical Method. (MRID #s 437825-01)[CBTS #s 16279 and 16681]{DP Barcode #s D219672 and D222000}

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and

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Thru: Michael S. Metzger, Chief
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INTRODUCTION

Dr. D.L. Kunkel, Coordinator, on behalf of the IR-4 Project and the State Experiment Station of Hawaii proposes a tolerance with regional registration only in Hawaii for the herbicide quizalofop-p ethyl ester, trade named Assure® II (ethyl(R)-2-[4-((6-chloroquinoxalin-2-yl)oxy)phenoxy] propionate), its acid metabolite quizalofop-p {R-(2-[4-((6-chloroquinoxalin-2-yl)oxy)phenoxy]) propanoic acid} and the S enantiomers of the ester and the acid, all expressed as quizalofop-p ethyl ester in or on the raw agricultural commodity (rac): pineapples at 0.1 ppm.

EXECUTIVE SUMMARY OF RESIDUE CHEMISTRY DEFICIENCIES

- NONE -

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CONCLUSIONS

1. CBTS Conclusion on **Product Chemistry/Chemical Identity**

CBTS concludes that after reviewing the confidential statement of formula (CSF) for the TGAI the impurities present in the TGAI quizalofop-p ethyl ester are not expected to present a residue problem in the subject crop pineapples when formulated into Assure® II and used as directed.

2. CBTS Conclusion on **Directions for Use/Labeling**

The petitioner has proposed an adequate set of directions for use of quizalofop-p methyl ester, formulated as Assure® II, in conjunction with an approved oil concentrate or a non-ionic surfactant on pineapples.

3. CBTS Conclusion on the **Nature of the Residue - Plants**

CBTS reiterates that the nature of the quizalofop-p ethyl ester residue in cottonseed, potatoes, soybeans, tomatoes and sugarbeets is adequately understood. The residues of concern are quizalofop-p ethyl ester and its acid metabolite, quizalofop-p, and the S enantiomers of both the ester and the acid, all expressed as quizalofop-p ethyl ester. We are translating these data to pineapples.

4. CBTS Conclusion on the **Nature of the Residue - Livestock**

The nature of the quizalofop ethyl ester residue in livestock is adequately understood. The residues of concern are quizalofop ethyl, quizalofop methyl, and quizalofop, all expressed as quizalofop ethyl.

5. CBTS Conclusion on **Confined Accumulation Studies on Rotational Crops**

The petitioner has characterized and identified over 50% of the residue in each of the rotational crops from the ^{14}C-quizalofop ethyl soil treatment. The nature of the residue in rotational crops is adequately understood and has the same metabolic pathways as identified above for tomatoes, cottonseed, soybeans, and sugar beets. The residues of concern are quizalofop ethyl and its acid metabolite.

6. CBTS Conclusions on the **Residue Analytical Method**

a. The petitioner has presented an adequate validated residue analytical method to gather the magnitude of the quizalofop-p residue data from crop field trials and in processed pineapple fractions.

b. The revised residue analytical method as presented in PP# 3F4268 has been submitted for a Tolerance Method Validation (TMV) in EPA laboratories. The Analytical Chemistry Branch (ACB) noted several deficiencies in the method. The registrant, DuPont, needs to respond to ACB's concern with a revised method before we can get the TMV back on track. CBTS reiterated that

the completion of the TMV is not a prerequisite for establishing the tolerance on pineapple.

7. CBTS Conclusions on **Storage Stability**

a. The petitioner has provided frozen storage stability data for quizalofop acid, phenols 2, 3, and 4 in cottonseeds and cotton processed commodities, snap bean pods and "straw," peas and pea forage, sugarbeet roots, and canola which show residues are stable for at least 2 years. The data are sufficient to support the magnitude of the residue crop field trial data submitted in this petition where samples were stored under similar conditions and for a shorter time. We are translating these data to pineapples.

b. A limited amount of frozen storage stability data for quizalofop-p and its acid metabolite on pineapples and pineapple processed fractions indicate that the parent and its acid metabolite are stable for at least 10 months.

8. CBTS Conclusions on **Magnitude of the Residue - Crop Field Trials**

a. When the number of crop field trials presented are reviewed against the data requirements for number of trials as described in the "EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances", June 1994, the petitioner appears to need to present additional quizalofop-p ethyl ester magnitude of the residue crop field trial data from 6 additional trials. However, since the petitioner generated exaggerated rate residue data showing no detectable residues and these trials were conducted prior to the 1994 data requirements, CBTS waives the requirement for 6 additional quizalofop-p pineapple field trials.

b. CBTS concludes that quizalofop and its metabolites, all expressed as quizalofop-p ethyl ester, are not expected to exceed the proposed 0.1 ppm tolerance on pineapples when Assure® II is used as directed.

9. CBTS Conclusion on **Magnitude of the Residue - Processed Food/ Feed**

The petitioner has conducted an adequate pineapple processing study using pineapples following an individual 2X exaggerated application with a 160 days PHI. No total quizalofop residues were detected in any of the processed fraction samples (juice and wet pulp or processed residue); thus no FAT is required.

10. CBTS Conclusions on **Magnitude of the Residue - Meat/Milk/ Poultry/Eggs**

a. The results of the quizalofop ethyl ester bovine feeding study show that finite residues will actually occur in milk and livestock tissues from the feeding of quizalofop ethyl ester treated racs or their processed feed items when Assure® II is

used as directed. The established quizalofop and quizalofop ethyl ester tolerances in milk, and in fat, meat, and meat by-products of cattle, goats, hogs, horses, and sheep are adequate and need not be increased from this additional use.

b. There are no poultry feed items in this petition, thus the established quizalofop and quizalofop ethyl ester tolerances in eggs, and in fat, meat, and meat by-products of poultry are adequate and need not be changed from this additional use.

11. CBTS Conclusion on Harmonization of Tolerances

Since there are no Canadian, Mexican, Codex MRLs/tolerances, compatibility is not a problem at this time.

RECOMMENDATIONS

Tox considerations permitting, CBTS recommends for the requested tolerance for the combined residues of the herbicide quizalofop-p ethyl ester, its acid metabolite quizalofop-p, and the S enantiomers of the ester and the acid, all expressed as quizalofop-p ethyl ester in or on pineapples at 0.1 ppm.

A DRES analysis may be initiated using the tolerance of 0.1 ppm in pineapples. If necessary for anticipated residues for chronic risk assessment use of the LOQ of 0.05 ppm is acceptable. There is no anticipation of concentration of residues in pineapple juice.

DETAILED CONSIDERATIONS

BACKGROUND

A letter signed by M.M. Chubb, Product Registration Manager for DuPont Agricultural Products, dated June 1, 1995, authorizes the Agency to refer to quizalofop-p ethyl ester data on file to support this petition.

CBTS has recommended for the established tolerance of the combined residues of the racemic mixture of quizalofop ethyl and its acid metabolite quizalofop, all expressed as quizalofop ethyl on soybeans at 0.05 ppm (see 40 CFR §180.441 [a]). A food additive tolerance (FAT) has been established for the combined residues of the racemic mixture of quizalofop ethyl on soybean flour at 0.5 ppm (see 40 CFR §185.5250) and feed additive tolerances have been established for combined residues of the racemic mixture on soybean hulls at 0.2 ppm, on soybean meal at 0.5 ppm, and on soybean soapstock at 1 ppm (see 40 CFR §186.5250). CBTS has also recommended for the established tolerance of combined residues of the R enantiomer quizalofop-p ethyl ester and its acid metabolite, quizalofop-p, and the S enantiomers of both the ester and the acid, all expressed as quizalofop-p ethyl ester on cottonseed at 0.05 ppm (see 40 CFR §180.441[c]).

In addition, CBTS has recommended for two Emergency Exemptions (Section 18) for use of quizalofop-p ethyl ester on mint hay at 5 ppm and mint oil at 0.05 ppm (see 93WA0008 and 93MT0004).

PRODUCT CHEMISTRY/CHEMICAL IDENTITY

CBTS concludes that after reviewing the results of the preliminary analysis of the TGAI (contains 98% active ingredient) as presented on the Confidential Statement of Formula (CSF) that the impurities present in the TGAI quizalofop-p ethyl ester are not expected to present a residue problem in the subject crops in this petition when formulated into Assure® II and used as directed (see PP# 3F3252/6H5479).

DIRECTIONS FOR USE/LABELING

Quizalofop-p ethyl ester is proposed for use as a herbicide to provide selective post-emergence control of annual grasses; eg, wild oats, foxtails, barnyardgrass, etc., and perennial grasses; eg, quackgrass, johnsongrass, etc.

The formulation to be used on pineapples is Assure® II Herbicide (EPA Reg. No. 352-541) containing quizalofop-p ethyl ester at 10.3%, or 0.88 lb a.i. per gallon. In ground applications, apply with standard fan or hollow cone nozzles, not with flood type nozzles. Also, in ground applications apply in a minimum of 10 gallons to 20 gallons per acre, and use either an EPA approved oil concentrate at a rate of 4 qts per 100 gallons (1-2%), or a non-ionic surfactant at a rate of 1 qt per 100 gallon (0.25%).

To control annual and perennial grasses in pineapples apply 29 to 60 ozs of Assure® II (0.165 to 0.41 ozs ai quizalofop-p ethyl ester per 1/2 gal) per acre per application up to 4 applications per crop growing season when the grasses are actively growing, usually in the 3 leaf to pre-boot stage. The maximum application to pineapples n a crop growing season is 60 ozs Assure® II (0.41 ozs ai) with a 160 day PHI.

The petitioner cautions that the cereal grains are "highly sensitive" to Assure II, thus care should be taken to avoid application when drift is likely. Assure II should not be applied through any irrigation system.

The petitioner has proposed an adequate set of directions for use of quizalofop-p methyl ester, formulated as Assure® II, in conjunction with an EPA approved oil concentrate or a non-ionic surfactant on pineapples.

NATURE OF THE RESIDUE - PLANTS

The registrant has previously provided plant metabolism studies for soybeans, cotton, potatoes, tomatoes, and sugarbeets (see PP# 3F4268 for review and summary).

In summary, quizalofop-p ethyl ester is metabolized by cleavage at three sites as follows (see structures in Appendix I):

1) Primary pathway is hydrolysis of the ethyl ester to form the quizalofop-p acid, then

2) Cleavage of the enol ether linkage in the acid between the phenyl and quinoxalinyl rings to form phenol 2 and phenol 4. Cleavage of the enol ether linkage in the intact quizalofop-p ethyl ester is a minor pathway that produces phenol 2 and phenol 3 which is the ester of phenol 4.

a. Phenols 2, 3, and 4 readily form plant glucose conjugates.

b. Some of the phenol 2 is hydroxylated to form hydroxyphenol 2, a minor metabolite.

c. Some phenol 3 is hydroxylated to phenol 4.

3) Cleavage of the ether linkage between the isopropanic group and the phenyl ring to form phenol 1.

a. Phenol 1 forms plant conjugates and/or

b. is cleaved at the enol ether linkage between the quinoxalinyl and phenyl rings to form phenol 2 (then some hydroxy phenol 2).

The plant metabolism data show that quizalofop-p ethyl ester does not translocate, but is rapidly hydrolyzed to the corresponding acid. Metabolism studies in soybeans using the racemic mixture quizalofop ethyl ester and the resolved D+ isomer show nearly identical pathways.

CBTS reiterates that the nature of the quizalofop-p ethyl ester residue in cottonseed, potatoes, tomatoes, soybeans, and sugarbeets is adequately understood. The residues of concern are quizalofop-p ethyl ester and its acid metabolite, quizalofop-p, and the S enantiomers of both the ester and the acid, all expressed as quizalofop-p ethyl ester. We are translating these data to pineapples.

NATURE OF THE RESIDUE - LIVESTOCK

^{14}C-phenyl and ^{14}C-quinoxaline quizalofop ethyl ester caprine and poultry metabolism studies have been submitted and reviewed.

In summary, the primary pathway in ruminants is hydrolysis of the ethyl ester to form the quizalofop-p acid, then methyl esterification to form the quizalofop methyl ester. Since neither phenol 1 or phenol 2 were detected, cleavage of the enol ether linkage in the acid between the phenyl and quinoxalinyl rings and cleavage of the ether linkage between the isopropanic group and the phenyl ring are not ruminant metabolic pathways.

In poultry, the primary metabolic pathway is also the hydrolysis of the ethyl ester to form the quizalofop-p acid, then methyl esterification to form the quizalofop methyl ester becomes a minor pathway. Poultry apparently recognize the free acid metabolite as a fatty acid and utilizes it in fatty acid chain elongation to form the quizalofop-pentanoic acid metabolite through a series of reactions involving acetyl Co-A, NAD/NADPH, and catalyzed by beta-hydroxyaryl dehydrogenase and enoyl reductase. Since neither phenol 1 or phenol 2 were detected, cleavage of the enol ether linkage in the acid between the phenyl and quinoxalinyl rings, and cleavage of the ether linkage between the isopropanic group and the phenyl ring are not poultry metabolic pathways.

The nature of the quizalofop ethyl ester residue in livestock is adequately understood. The residues of concern are quizalofop ethyl, quizalofop methyl, and quizalofop, all expressed as quizalofop ethyl.

CONFINED ACCUMULATION STUDIES ON ROTATIONAL CROPS

[Phenyl-^{14}C]- and [quinoxaline-^{14}C]-quizalofop ethyl treated soils were aged 30 and 62 days before planting with the rotational crops red beets, lettuce, wheat, peanuts, and cotton. The petitioner has characterized and identified over 50% of the residue in each of the rotational crops from the phenyl and quinoxaline labeled quizalofop ethyl soil treatment and has confirmed the hydrolysis of the ethyl ester, and the cleavage of the enol and ether linkages metabolic pathways. The data support a 120 day plantback interval.

The nature of the residue in rotational crops is adequately understood and is the same as identified above for tomatoes, cottonseed, soybeans, and sugar beets. The residues of concern are quizalofop ethyl and its acid metabolite.

RESIDUE ANALYTICAL METHOD

The petitioner presented a copy of the method titled "Determination of DPX-79376, DPX-79376 Acid and Conjugates as DPX-79376 Acid in Cottonseed and Fractions treated with Assure II Herbicide" by O.R. Hunt and coded DuPont Report Number AMR 1853-90 (see **MRID # 433140-01**) to gather the magnitude of the residue data crop for field trials and processed fractions. The method is referred to as LAN-1 and has been reviewed in PP# 3F4268. When the samples were analyzed minor modifications were made for the substrate pineapples by the Hawaiian Sugar Planters' Association in their method titled "Determination of Quizalofop-ethyl (Assure® II) in Pineapples by LC with UV Detection" by M. Zhou and coded A-02-92.

In summary, 10 grams of pineapple sample were extracted 2 X 70 mls with ACN/1% HOAc (3/1, v/v). The combined aqueous extract was enzymatically hydrolyzed with cellulase, esterase, and beta-glucosidase, and cleaned up on a prep or cleanup HPLC column, reanalyzed by HPLC using a Zorbax® RX C-8, 5 mu 4.6 X 250 mm column with the mobile phase of 22% ACN/K_2HPO_4 at 1 ml/min flow rate and detection by UV at 238 nm. Quantitation was by peak height. Acceptable linearity curves were presented.

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The limit of quantitation (LOQ) is 0.05 ppm and the limit of detection being 0.01-0.02 ppm. These values were confirmed from reviewing the supporting chromatographic data.

Control samples of the rac pineapple, slices, and the processed fractions juice and ionex juice, wet bran (pulp), and skin were fortified with quizalofop ethyl ester and the acid metabolite at 0.05 and 0.5 ppm. The dried bran was fortified at 0.1 and 1 ppm. Overall quizalofop ethyl ester recoveries ranged from 76 to 115%, averaging 95 ± 10% and for the acid metabolite ranged from 70 to 116%, averaging 89 ± 12%, n = 46.

Concurrent quizalofop and quizalofop-p recoveries from pineapples and pineapple processed fractions spiked at 0.05 ppm and 0.1 ppm in dried bran ranged from 84 to 112%, averaging 97 ± 10% for the acid; and from 77 to 119% averaging 97 ± 12, n = 11, for the parent compound. The petitioner has presented an adequate validated residue analytical method to gather the magnitude of the residue data from crop field trials and in processed pineapple fractions.

The revised residue analytical method as presented in PP# 3F4268 has been submitted for a Tolerance Method Validation (TMV) in EPA laboratories. The Analytical Chemistry Branch (ACB) noted several deficiencies in the method. The registrant, DuPont, needs to respond to ACB's concern with a revised method before we can get the TMV back on track. CBTS reiterated that the completion of the TMV is not a prerequisite for establishing the tolerance on pineapple.

STORAGE STABILITY

Storage stability data have been previously submitted for soybeans and cottonseed (high oil content commodities) which show that quizalofop ethyl ester, the free acid, and phenols 1, 2, and 4 metabolites are stable in frozen storage for at least 5 1/2 months.

The petitioner presented limited storage stability data for quizalofop-p and its acid metabolite in pineapple, slices, beverage juice and IX juice, pulp, bran, and unprocessed skins fortified at 0.05 ppm and stored from 7 to 10 months. Quizalofop-p and its acid metabolite were shown to be stable in pineapples and pineapples processed fractions for at least 10 months.

The petitioner has also provided frozen storage stability data for quizalofop acid, phenols 2, 3, and 4 in cottonseeds and cotton processed commodities, snap bean pods and "straw," peas and pea forage, sugarbeet roots, and canola which show residues are stable for at least 2 years. The data are sufficient to support the magnitude of the residue crop field trial data submitted in this petition where samples were stored under similar conditions and for a shorter time. We are translating these data to pineapples.

MAGNITUDE OF THE RESIDUE - CROP FIELD TRIALS (MRID # 437825-01)

The petitioner presented quizalofop-p ethyl ester magnitude of the residue data on pineapples and pineapple processed fractions in a

study titled "Quizalofop-p Ethyl Ester: Magnitude of Residues on Pineapple" by D. Kunkel dated August 23, 1995, and coded laboratory project number 3893.91-HSR03.

The petitioner presented total quizalofop-p magnitude of the residue data on pineapples from 2 crop field trials in Hawaii (one on Oahu and the other on Maui) for the 1991-2 crop year on 1 variety. When the number of crop field trials presented are reviewed against the data requirements for number of trials as described in the "EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances", June 1994, the petitioner appears to need to present additional quizalofop-p ethyl ester magnitude of the residue crop field trial data from 6 additional trials. However, since the petitioner generated exaggerated rate residue data showing no detectable residues and these trials were conducted prior to the 1994 data requirements, CBTS waives the requirement for 6 additional quizalofop-p pineapple field trials.

Each trial had a control plot and 2 test plots. One pineapple test plot received a single ground foliar spray at a rate of 0.4 oz ai (1X)/acre in 197 gal water/acre 13 months after planting along with the surfactant. The other pineapple test plot received a single ground foliar spray at a rate of 0.8 oz ai (2X)/acre. Both the 1X and 2X applications were done at the same time in late 1991.

Four mature rac pineapples were harvested at 160 days PHI in May 1992 from each test subplot plus 6 pineapples were harvested for a processing study. Samples were delivered to the lab in the day of harvest and prepared promptly for analysis, then frozen and remained frozen until analysis.

Residues of quizalofop-p and its acid metabolite were not detected to the LD of 0.02 ppm in any of the control and treated rac pineapples.

At this time we conclude that quizalofop and its metabolites, all expressed as quizalofop-p ethyl ester, are not expected to exceed the proposed 0.1 ppm tolerance on pineapples when Assure® II is used as directed.

MAGNITUDE OF THE RESIDUE - PROCESSED FOOD/FEED

The petitioner submitted the results of a quizalofop pineapple processing study in the same document with the crop field trial residue data.

The pineapples from both 1X trials and the 2X Maui trial were processed by the Maui Pineapple Company, Ltd. using a small scale commercial process into tidbits, slices, chunks, crush pineapple, beverage juice, IX syrup or juice, feed pulp, and bran. No quizalofop-p ethyl ester or its acid metabolite residues were detected in the rac, slices, beverage juice and IX juice, pulp, bran, or unprocessed skins to the LOQ of < 0.05 ppm and 0.1 ppm in bran.

The petitioner has conducted an adequate pineapple processing study using pineapples following an individual 2X exaggerated application with a 160 days PHI. No total quizalofop residues were detected in any of the processed fraction samples; thus no FAT is required.

MAGNITUDE OF THE RESIDUE - MEAT/MILK/POULTRY/EGGS

RUMINANTS

A ruminant feeding study has been submitted and reviewed. In summary, 3 group of 3 lactating dairy cows (plus a control group) were fed 0.1, 0.5, and 5.0 ppm quizalofop ethyl ester encapsulated for 28 consecutive days. Milk was collected daily and a sub-sample was divided into skim milk and cream. Two cows were sacrificed after 28 days with samples of fat, skeletal muscle, liver, and kidney being collected and analyzed. The remaining cow in each test group was fed a regular diet without encapsulated quizalofop ethyl ester for 7 additional days before sacrifice. Whole milk, skim milk, and cream from the control, and the 0.1 and 0.5 ppm dose groups show no quizalofop to <0.02 ppm (0.05 ppm in cream). From the 5 ppm dose quizalofop residues ranged from 0.01 to 0.02 ppm in whole milk, and when these samples were separated into cream and skim milk the quizalofop partitioned into the cream with residues plateauing at 0.26 to 0.31 ppm. No quizalofop to < 0.02 ppm was detected in skeletal muscle, and to < 0.05 ppm was detected in any liver or fat sample from any of the 3 doses. Quizalofop was detected in one kidney sample at 0.05 ppm from the 5 ppm dose.

The bovine feed item in this petition is processed residue; also known as wet bran and is a wet paste byproduct from the fresh cut product line that includes pineapple tops (minus crown), bottoms, peels, any trimmings with peel cut up, and the pulp (left after squeezing for juice). It can be included up to 30% in beef cattle diets and 20% in dairy cattle diets for potential dietary burdens of 0.12 and 0.08 ppm respectively.

From the feed stuff in this petition plus all of the feed stuffs in co-pending petitions, all of the feed stuffs in cattle diets can be treated with quizalofop ethyl ester. A theoretical beef cattle diet consisting of pineapple processed residue, bean and pea forage, pea hay, and sugarbeet tops in various combinations is highly artificial, but none-the-less maximizes the potential quizalofop exposure up to 2.4 ppm. Substitutions of other feed items and varying their percentages in the diets would give a lower bovine dietary quizalofop burden.

The results of the quizalofop ethyl ester bovine feeding study show that finite residues will actually occur in milk and tissues from the feeding of quizalofop ethyl ester treated racs or their processed feed items when Assure® II is used as directed. The established quizalofop and quizalofop ethyl ester tolerance in milk, and in fat, meat, and meat by-products of cattle, goats, hogs, horse, and sheep are adequate and need not be increased from this additional use.

POULTRY

There are no poultry feed items in this petition, thus the established quizalofop and quizalofop ethyl ester in eggs, and in fat, meat, and meat by-products of poultry are adequate and need not be changed from this additional use.

HARMONIZATION OF TOLERANCES

An INTERNATIONAL RESIDUE LIMIT STATUS SHEET (IRLS) is attached to this review. Since there are no Canadian, Mexican, Codex MRLs/tolerances, compatibility is not a problem at this time.

Appendix I: Structures of Quizalofop-p and its Metabolites

cc:R.F.,Circu,Reviewer(FDG),PP#5E4590.
7509C:CBTS:Reviewer(FDG):CM#2:Rm804Q:305-5826:FDG:1/23/96:edit:fdg:1/26/96.
RDI:TPT-1:1/25/96:BrSrSci:RALoranger:1/25/96:BrCh:MSMetzger:1/26/96.