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

23 MAR 1987

EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#6F3387/6H5499 Metalaxyl on Fruiting Vegetables (except Curcurbits), Sugar Beets and Sugar Beet Tops. Evaluation of March 6 and 10, 1987, Amendments. (No Assession Number) [RCB #2037 and #2039]

FROM: Francis D. Griffith Jr., Chemist
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THRU: Charles L. Trichilo, Chief
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TO: Lois A. Rossi (Acting PM-21)
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Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

The review of these amendments are being expedited at the request of Edwin F. Tinsworth, Director of the Registration Division in his memorandum dated February 11, 1987, to John W. Melone, Director of the Hazard Evaluation Division.

Ciba-Geigy Corporation, Agricultural Division has submitted these amendments consisting of cover letters and a supplementary Section D (a description of the sugar beet processing study with results, the analytical method, validation data, and chromatographic data). The amendments have been submitted in response to deficiencies outlined in our review of metalaxyl (trade named Ridomil® and Apron®) in fruiting vegetables and sugar beets by F. D. Griffith, Jr. on March 13, 1987. The deficiencies are listed below as they appeared in the March 1987, review followed by the petitioner's responses then RCB comments and conclusions.

Deficiency 1. Submit a complete description of the analytical method used to generate the metalaxyl residue data on sugar beets, sugar, molasses and dehydrated beet pulp. The summary is not sufficiently complete to judge the method.

Petitioner's Response

In Volume 4 of 4 this submission the petitioner has submitted an updated description of analytical method for metalaxyl.

RCB Comments

The method used to gather the metalaxyl residue data on sugar beets, sugar, molasses, and dehydrated beet pulp is coded AG-395, dated December 7, 1982, signed by K. Balasubramanian and R. Perez, and titled "Improved Method for the Determination of Total Residues of Metalaxyl in Crops as 2,6-dimethylaniline." An earlier edition of this has been previously submitted and reviewed (see memorandum PP#3F2918, K. Arne, December 13, 1983). RCB judged the method to be significantly different from methods 330 and 348, thus a method tryout (MTO) was requested. The results of the MTO (see memorandum PP#3F2918, P. Jung, July 9, 1984) showed EPA recoveries of total metalaxyl from peanuts and peanut hay range from 62 percent to 102 percent at spike levels of 0.05 ppm, 0.5 ppm, and 5 ppm. This methods has not had a MTO using sugar beets and sugar beet processed commodities as matricies. The method has been submitted to FDA but is not presently in PAM-II.

In summary, method AG-395, dry crop version, involved refluxing ten grams of sugar beets and sugar beet processed products for two hours in 100 mL of methanol/water (80/20, v/v). Filter through Whatman 2V filter paper then remove a two gram aliquot equivalent. Rotoevaporate to dryness then dissolve the residue in one mL H_2O and ten mL of methanesulfonic acid. Reflux for 15 minutes. The petitioner cautions a 20 minute reflux will degrade 2,6-dimethylaniline. Cool, then add 15 mL hexane and 25 mL of 25 percent NaOH through the top of the condenser. Be sure the pH > 8.0. The steam distillation apparatus is a modification of the equipment proposed by Veith and Kiwus and is commerically available from Ace Glass Co.(telcon EPA-Ciba,March 16, 1987). The distillation time is approximately 1 1/4 hours. The solution is then frozen. Cleanup is by silica SepPak®. The hexane is poured off the frozen water into the syringe then force through the SepPak® at a rate < 5 ml/min. The 2,6-dimethylaniline is recovered from the SepPak® with 18 mL CH_2Cl_2. The derivative is formed by adding 200 uL of trifluoroacetic acid (TFA), then rotoevaporate in a 15 °C, not 18 °C or 20 °C, water bath to just dryness. Dryness is essential as traces of TFA will cause losses. Take up in 2.0 mL tolune and transfer the tolune to a HP autosampler vial. The instrument used was a Hewlett Packard (HP) gas chromatograph, model 5880, equipped with a N/P detector and a capillary column. The columns were either a fused silica 0.25 um coating of SE-54 in a 0.2 mm x 25 m column or a wide bore 0.32 mm x 30 m fused silica column with a 0.25 um coating of DX-4. The petitioner has adequate run tables and used suitable temperature programming.

Confirmation of residues is by GC/MS using a Finnigan GC/MS, model 3200, operated in the CI mode with CH_4 as the reactant and carrier gas. The column is a glass, 1.2 m x 2 mm (id), packed with 3 percent Dexsil-300 on Gas Chrom Q (80/100 mesh) and operated at 100 °C. The fragment ion DMA is measured at m/e of 122 (the m + 1 ion).

The limit of metalaxyl sensitivity or reliable quantification is < 0.05 ppm. Quantitation is by the HP-1000 Lab Automation computer system. An electronic calculator such as a TI-55 is also adequate. The peak heights are used for comparison of standards in a range from 0.04 ng to 2.0 ng to unknowns for software calculations. Corrections are made for recoveries but not controls; and a factor 1.188 is used to convert DMA-TFA detected to metalaxyl equivalents. The petitioner has now provided all of the necessary details for RCB to judge the method.

RCB Conclusion

The written description of the method plus a Telcon (F.D. Griffith, EPA - L.G. Ballantine, Ciba) on March 16 have provided RCB with a complete description of the analytical method.

Deficiency one is now resolved.

Deficiency 2. The petitioner needs to provide a complete set of metalaxyl validation data using method AG-395 for sugar beets, sugar, molasses,and dehydrated beet pulp.

Petitioner's Response

In Volume 2 of 4 of this submission the petitioner has provided validation data. This part of the submission also included Ciba-Geigy document AG-A 9908. The title of the report is "Total Metalaxyl Residues in Sugar Beet Fractions Following Application of Ridomil® 2E and Ridomil MZ58 (Magnitude of Residues)" by B. Gold and dated February 25, 1987.

RCB Comments

Sugar Beet Roots control sample was spiked with 0.2 ppm metalaxyl and a recovery of 97% using method AG-395 (discussed above) was obtained. In the telcon (ibid) RCB learned there are additional metalaxyl recovery data on sugar beets with spikes ranging from 0.05 ppm to 0.5 ppm and corresponding recoveries ranging from 75% to 97%. Sugar beet pulp control sample was spiked with 0.1 ppm metalaxyl and had a recovery of 91%. Sugar control sample was spiked with metalaxyl at 0.05 ppm with recovery of 71%. Molasses control sample was spiked at 0.1 ppm. The 56% recovery is somewhat lower then RCB generally accepts but considering the matrix RCB will accept the data.

The petitioner also provided metalaxyl recovery data from cossettes. At the 0.1 ppm fortification level recoveries were 40% and 55%. RCB can not explain these recoveries in view of the 97% recovery on sugar beets, per se. In the telcon (ibid) the petitioner is aware of the problem and, at this time, could not offer an explanation, but is working to resolve the problem prior submission of any additional metalaxyl residue data on sugar beets.

RCB does not need additional method validation data for metalaxyl on sugar beets and sugar beet commodities to judge the proposed tolerances.

RCB Conclusion

The petitioner has provided a complete set of metalaxyl recovery/validation data using method AG-395 for sugar beets, sugar, molasses, and dehydrated beet pulp.

Deficiency two is thus resolved.

Deficiency 3. The petitioner needs to supply all supporting chromatographic data in order for RCB to determine the appropriate concentration factor thus judge the adequacy of the proposed food additive metalaxyl tolerance (FAT) for molasses.

Petitioner's Response

In the March 10, 1987, amendment the petitioner supplied the requested supporting chromatographic data.

RCB Comments

The petitioner supplied twelve photocopies of chromatograms for metalaxyl derivatized standards ranging from 0.02 ng to 0.5 ng. Copies of four control sample chromatograms were presented. RCB concludes there are no unidentified analytical responses (UAR's) where metalaxyl-TFA elutes. Metalaxyl spikes at various fortification levels in the control samples could be quantatated. In both the controls and spike samples UAR's are not a problem. Likewise in the eight field incured residue sample chromatograms UAR's are not a qualitative or quantitative problem. RCB observes the limit of detection is closer to 0.01 ppm and the limit of sensitivity or reliable quantification is <0.05 ppm. The petitioner provided no copies of sugar chromatograms. In the telcon (ibid) RCB was assured sugar chromatograms contained lower and smaller UAR's. This is as RCB expects, thus no additional chromatograms for metalaxyl in sugar are necessary. Reviewing the chromatogram for sugar beet sample, 2 - 1AB, RCB observes metalaxyl being present at a 0.035 ppm level. Using the 0.035 ppm as the indication of the "true" residue level in the rac the concentration factor is 10X. Thus the highest concentration factor for metalaxyl in sugar beets processed into molasses is 10X, and not 5.25X.

For this petition RCB needs no additional supporting chromatographic data to determine the appropriate concentration factors for the proposed food additive metalaxyl tolerances. The petitioner's 1.0 ppm metalaxyl in molasses is adequate.

RCB Conclusion

The petitioner has presented the requested supporting chromatographic data. The appropriate concentration factor for metalaxyl from sugar beets to molasses to 10X. The proposed FAT for metalaxyl in molasses at 1.0 ppm is adequate. RCB now concludes the petitioner has presented a well described, validated analytical method with supporting chromatograms and this method is suitable to gather the metalaxyl residue data on sugar beets and sugar beet commodities molasses, dehydrated beet pulp, and sugar.

Deficiency 3 is thus resolved

Deficiency 4. RCB can not judge any results of the metalaxyl sugar beet processing study until the petitioner has provided a complete description (including flowchart, if applicable) of the actual process and, if appropriate, describe how and why it differs from the standard commerical sugar beet process. It is possible that most, if not all, of the information RCB needs to complete its review of the study from planting of seeds to review of metalaxyl results in the processed commodities is in Ciba-Geigy document coded AG-A 9908,01. The petitioner is encouraged to submit this document for review.

Petitioner Response

The petitioner provided a description of the sugar beet processing study and a flow chart of the process used to generate the commodities in this study.

RCB Comments

The raw sugar beets were shipped to Spreckels Sugar Division of Amstar Corporation. The samples were held three to five days in cold storage prior to processing. The beets were processed in batches of 260 lbs. each. The sugar beet processing is summarized as follows:

The beets were first thoroughly washed then sent to the slicer. The whirling knives sliced the beets into thin strips called cossettes. The cossettes were then fed into the diffuser where the hot water removes the sugar. This solution is called raw juice. The raw thin juice is purified in the Dorr Carbonater where lime and CO_2 are added to remove/precipitate impurities. This solution is called thin juice. After filtration the thin juice underwent a second purification step in the lab prior to evaporation.

In the commerical process there were two evaporation steps to form a thick juice. RCB does not consider this change between lab processing and commerical processing significant enough to change residue results. A final filtration removes all solid particles. Sugar is formed by boiling the juice under vacuum. The resulting mass of crystals and liquid is called fillmass. The fillmass is then spun and washed in a centrifuge. The crystals left are white and are now "pure" sugar (sucrose). The separated liquid is the molasses. The commerical process takes the raw sugar and drys it by tumbling in warm air in a rotating drum called a granulator.

At the diffuser the mass left over after removing the raw juice is the wet beet pulp. In this process the wet pulp is sent to a press. The press water is added to the raw juice. The remaining pulp is then dried. The commerical beet pulp can be a livestock feed either wet or dried. Occasionally some of the molasses is added back into the pulp prior to final drying and distribution into livestock feed channels.

RCB considers there are no significant differences between commercial sugar beet processing and the processing of these test metalaxyl treated sugar beets into sugar, molasses, and dehydrated beet pulp. RCB found the petitioner's flow chart a valuable aid in understanding how his sugar beets were processed in the lab.

RCB now has the suggested description of the sugar beet processing. The sugar beet processed commodities were prepared by an acceptable process.

RCB Conclusion

RCB concludes the petitioner has conducted an acceptable metalaxyl in sugar beets processing study and generated valid residue data using approved methods.

RCB concludes that a FAT is appropriate only for molasses. The metalaxyl concentration factor for sugar beets to molasses is 10X. The petitioner has proposed metalaxyl tolerances for sugar beets and sugar beet tops at 0.1 ppm from a seed treatment use. The petitioner has proposed a FAT of 1.0 ppm metalaxyl in molasses from sugar beets seeds treated with metalaxyl. Metalaxyl FAT's are not necessary for sugar and dehydrated sugar beet pulp. RCB does not expects the proposed tolerances to be exceeded.

Deficiency 4 is thus resolved.

Other Considerations

In our original review dated September 26, 1986 (which see) RCB determined there was adequate metalaxyl storage stability data to support this petition.

Volume 3 of 4 of this submission contains additional storage stability data for metalaxyl. The title of the study is "Stability and Accountability of Residues of Metalaxyl and Selected Metabolites Using Analytical Method AG-395 (Storage Stability)" by B. Gold and dated May 28, 1986. Ciba's code for this study is ABR-86044.

The petitioner prepared homogenous samples of apples, cabbage, lettuce, potatoes and strawberries. Samples of each of these substrates were fortified separately with 1.0 ppm of metalaxyl; and the metabolites CGA-62862 [N-2,6-dimethyl-phenyl)-N-(methoxyacetyl) alanine], CGA-67869 [N-(2,6-dimethyl-phenyl)-N-(hydroxyacetyl) alanine methyl ester], CGA-107955 [N-(2,6-dimethylphenyl)-N-(hydroxyacetyl) alanine], CGA-37734 [N-(2,6-dimethylphenyl)-2-hydroxyacetamide], and CGA-94689 [N-[-2-(hydroxymethyl)-6-methylphenyl]-N-(methyloxyacetyl) alanine methyl ester]. The parent metalaxyl and each metabolite was added to the samples in an acetone solution. The acetone was allowed to evaporate, then the jars were sealed and stored in a freezer at - 15°C.

Samples were analyzed at zero day, six months, and at twelve months. The petitioner used the wet crop version of method AG-395 to gather the residue data (see memo dated September 26, 1986). Duplicate stored samples plus a control sample and a fortified sample were analyzed as a set.

Metalaxyl recovery results at a zero day storage period were all 1.0 ppm, at six months storage metalaxyl ranged from 0.93 ppm to 1.1 ppm, and at twelve months storage ranged from 0.98 ppm to 1.3 ppm. Metalaxyl at 1 ppm is stable for at lease twelve months in apples, cabbage, lettuce, potatoes and strawberries.

Metabolite CGA-62862 recovery results at zero day storage were all 1.0 ppm, at six months storage ranged from 0.94 ppm to 1.2 ppm, and at twelve months ranged 0.96 ppm to 1.1 ppm. CGA-62862 at 1.0 ppm is stable for at least twelve months in apples, cabbage, lettuce, potatoes, and strawberries.

Metabolite CGA-67869 recovery results at zero day storage were all 1.0 ppm, at six months storage ranged from 0.86 ppm to 1.2 ppm, and at twelve months storage ranged from 0.90 ppm to 1.2 ppm. CGA-67869 at 1 ppm is stable for at least twelve months in apples, cabbage, lettuce, potatoes and strawberries.

Metabolite CGA-107955 recovery results at zero day storage were either 0.99 ppm or 1.0 pm, at six months storage ranged from 0.84 ppm to 1.3 ppm and at twelve months storage ranged from 0.86 ppm to 1.0 ppm. CGA-107955 at 1 ppm is stable for at least twelve months in apples, cabbage, lettuce, potatoes, and strawberries.

Metabolite CGA-37734 recovery results at zero day storage were at the 1 ppm level, at six months storage results ranged from 0.77 ppm to 1.4 ppm and at twelve months results ranged from 0.91 ppm to 1.3 ppm. CGA-37734 at 1 ppm is stable for at least twelve months in apples, cabbage, lettuce, potatoes, and strawberries.

Metabolite CGA-94689 recovery results at zero days storage were 0.98 ppm to 1.0 ppm, at 6 months results ranged from 0.67 ppm to 1.1 ppm, and at twelve months storage results ranged 0.72 ppm to 1.1 ppm. RCB notes that metabolite CGA-94689 storage stability results are less in cabbage, lettue, and potatoes than in strawberries and apples. RCB does not consider the metabolite CGA-94689 storage stability results in cabbage, lettuce, and potatoes to warrant correction as only one recovery was less the 70% (at 67%). Thus RCB concluded metabolite CGA-94689 at 1 ppm is stable for at least twelve months in apples and strawberries; and stable for twelve months in cabbage, lettuce, and potatoes.

The petitioner has provided supplementary storage stability data for metalaxyl and five of its metabolites in a variety of matrices. Method AG-395 gives acceptable accountability for these six compounds in the five matrices during the period of freezer storage. RCB concludes metalaxyl and five of its metabolites are stable at -15°C for at least twelve months in apples, cabbage, lettuce, potatoes, and strawberies.

An updated Interational Residue Limit (IRL) status sheet was attached to the March 13, 1987, amendment review.

RCB Recommendation

There being no further residue chemistry deficiencies associated with this petition RCB makes the following recommendations; TOX Branch and EAB considerations permitting:

Since residues are not expected to exceed the proposed tolerance under the proposed conditions of use RCB recommends for the 1.0 ppm metalaxyl tolerance on the crop group Fruiting Vegetables (except Cucurbits) and recommends for the Feed Additive Tolerance of 20 ppm metalaxyl on tomato pomace (wet or dry).

Since residues are not expected to exceed the proposed tolerance under the proposed condition of use RCB recommends for the 0.1 ppm metalaxyl tolerance on sugar beets and sugar beet tops, and recommends for the FAT of 1.0 ppm metalaxyl in sugar beet molasses.

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