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

JUL 30 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PP#9F3743 - Clethodim (Select®) in/on Soybeans, Cottonseed,and Animal Commodities. Evaluation of the Petition Method Validation (PMV) Report on the Compound Specific Method. (No MRID#) [No CBTS#] {No HED Project#]

FROM: Francis D. Griffith, Jr., Chemist
Chemistry Branch I-Tolerance Support
Health Effects Division (H-7509C)

THRU: Richard D. Schmitt, Ph.D., Chief
Chemistry Branch I-Tolerance Support
Health Effects Division (H-7509C)

TO: Joanne I. Miller, PM-23
Fungicide-Herbicide Branch
Registration Division (H-7505C)

and

Donald A. Marlow, Chief
Analytical Chemistry Branch
Biological and Economic Analysis Division (H7503C)

EXECUTIVE SUMMARY OF DEFICIENCIES

- Rewrite the clethodim compound specific method, RM-26D-1, per ACB recommendations.
- Provide additional method validation data for the rewritten method for the same clethodim metabolites at the same fortification levels in the same matrices as were used in the EPA Petition Method validation.

Chemistry Branch I-Tolerance Support (CBTS) has been informed by the Analytical Chemistry Section, Analytical Chemistry Branch (ACB) of the completion of the requested clethodim compound specific (or confirmatory) method PMV. The

results of the PMV were reported by Douglas Swineford and Alex Krynitsky in their memorandum dated July 10, 1991.

The compound specific method PMV was requested for metabolites of clethodim or Select® (E-2-[-1-(((3-chloro-2-propenyl)-oxy)-imino)-propyl]-5-[2-ethylthio]-propyl-3-hydroxy-2-cyclohene-1-one)in the presence of equal amounts of sethoxydim or Poast® metabolites in soybeans, beef liver, and milk (see memo by F.D.Griffith, Jr., dated May 9, 1991 to ACB/BEAD). The compound specific method PMV for Clethodim metabolites in soybeans, beef liver, and milk was requested for the Valent Method RM-26D-1 dated December 14, 1990 and titled "Confirmatory Method for the Determination of Clethodim and Clethodim metabolites in Crops, Animal Tissue, Milk and Eggs, Supplemental to: Confirmatory Method for Determination of Clethodim Metabolites in Crops."

The PMV was conducted using the method as revised by the petitioner, and as provided by CBTS. Three major plus six minor modifications were made to the residue analytical method by ACB. The method as prepared by Valent <u>failed</u> the PMV. CBTS agrees with ACB that all 9 modifications are necessary for the clethodim metabolites compound specific method to satisfactorily recover and separate the clethodim and sethoxydim metabolites from soybeans, beef liver and milk.

The first major modification was to increase the amount of m-chloroperbenzoic acid and sodium thiosulfate in the oxidation step. The ACB lab could not obtain satisfactorily derivatized standards using the petitioner's suggested amount of reagents. Secondly, ACB had to reinsert the base wash step into the animal and milk part of the method. Without this step clethodim recoveries were essentially zero from meat and milk. The third major modification was to change from a Silica gel Sep Pak to a macro silica gel column cleanup. As the method was written the analytes of interest eluted off the Sep Pak in the discard fraction; thus, the recovery of clethodim metabolites was essentially zero. Once ACB switched to a macro silica gel column clethodim metabolites recoveries were acceptable. CB agrees with ACB that each batch of silica gel needs to be calibrated prior to its use in the clethodim metabolites compound specific method.

CB agrees with ACB's adding of a course glass fiber filter on top of the Whatman #42 filter to increase the speed of filtration; otherwise there is a risk of metabolite loss. It should be normal laboratory procedure to rinse the Na_2SO_4 with CH_2C1_2. ACB recommend the extract <u>Not</u> be taken to dryness prior to the oxidation step to avoid loss. CB agrees. In the determinative step ACB switched the UV wavelength for monitoring maximum absorbance to 266 nm for milk and soybeans, and to 270 nm for beef liver. We agree this change will improve the method's performance. ACB's suggestions for preparation of diazomethane are to be written into the revised method. While it is a minor point ACB's suggestion to add solid NaCl to the round bottom

flask instead of the separatory funnel is important. Solid NaCl can destroy teflon stopcocks in the separatory funnel.

ACB did not determine a limit of detection (LD) per se. The petitioner's claimed LD's were validated; thus, they now become a limit of sensitivity or quantitation. Based on the HPLC chromatograms the new LD's are estimated at 0.03 ppm in soybeans for clethodim sulfoxide and 5-OH clethodim sulfoxide, 0.05 ppm for sethoxydim sulfoxide, and at 1 ppm 5-hydroxy sethoxydim sulfoxide. In whole milk the new estimated LD's are 0.007 ppm for clethodim sulfoxide, S-methyl clethodim sulfoxide and sethoxydim sulfoxide. For beef liver the LD is 0.05 for clethodim sulfoxide and sethoxydim sulfoxide. The petitioner needs to confirm these limits of detection.

CBTS requested the clethodim compound specific method be validated at 0.05 ppm, 1.0 ppm, and 5.0 ppm in soybeans for clethodim sulfoxide and 5-OH clethodim sulfoxide. Plus, at the 5 ppm level we requested validation to show that if either 5-OH sethoxydim sulfoxide or sethoxydim sulfoxide were present then we could qualitatively and with reasonable quantitation separate clethodim metabolites from sethoxydim metabolites. Clethodim sulfoxide recoveries ranged from 65% to 111% (n=2 at each level). 5-OH clethodim sulfoxide recoveries ranged from 83% to 120% (n=2 at each level). Separation of clethodim from sethoxydim was not a problem. Sethoxydim sulfoxide recoveries at 5 ppm spike were 78% and 108%. 5-OH sethoxydim sulfoxide recoveries at the 5 ppm spike were 93.6% and 171%.

In beef liver CB requested the clethodim compound specific method be validated at only 0.2 ppm for clethodim sulfoxide and sethoxydim sulfoxide. Clethodim sulfoxide recoveries were 63.5% and 72.5%. Sethoxydim sulfoxide recoveries were 35% and 46%. Sethoxydim sulfoxide can be separated from clethodim sulfoxide in beef liver without any problem.

For milk CB requested the clethodim compound specific method be validated at 0.02 ppm and 0.05 ppm for clethodim sulfoxide and S-methyl clethodim sulfoxide. Plus at the 0.05 ppm fortification level we requested validation to show that if sethoxydim sulfoxide was present, then we could separate the two compounds qualitatively and with reasonable quantitation. Clethodim sulfoxide recoveries ranged from 55% to 101%, S-methyl clethodim sulfoxide recoveries ranged from 44.5% to 93%. Recoveries of the S-methyl clethodim sulfoxide are generally lower then we like for an enforcement procedure. However, acceptable quantitation can be achieved with the common moiety method. Recoveries of sethoxydim sulfoxide were 44% and 62%.

The wide range of sethoxydim sulfoxide recoveries is not a problem as the method is to confirm clethodim, not sethoxydim recoveries. Clethodim recoveries are generally quantitative and

there is complete qualitative separation from sethoxydim. CB does not consider this a problem as the common moiety clethodim method provides adequate quantitation of residues.

The petitioner's method proposed use of cloproxidim sulfoxide as the internal standard. We note that cloproxidim sulfoxide recoveries were erratic, generally lower than the compound of interest. CB agrees with ACB that in most cases use of the internal standard would over correct and give higher values than were actually present. In the rewritten method CB suggests all mention of the use of any internal standard with the clethodim metabolites compound specific method be deleted.

CB notes that the clethodim and sethoxydim recovery data reviewed above were generated with ACB's revised method. The method as presented by Valent gave zero recovery. Thus, there has not been a successful PMV with the petitioner's method as written. At this point EPA has a method with only one set of recovery values. Valent's method, RM-26-D-1, is not suitable to gather residue data or enforce any proposed tolerance as written.

The S-methyl clethodim sulfoxide and clethodim sulfoxide are currently available from EPA's Pesticides and Industrial Chemical rapacity at Research Triangle Park, N.C. The sethoxydim metabolites and the 5-OH clethodim sulfoxide were received from Chevron Chemical Company Richmond California. The petitioner is reminded these standards must be available from the EPA Repository for distribution to government enforcement laboratories prior to any favorable recommendation for a tolerance.

ACB reports that two skilled analysts require at least 24 hours to prepare 6 samples for HPLC analysis plus 50 minutes for each sample injection using ACB's modified version. CBTS considers this time frame is marginally satisfactory for a confirmatory method used in regulatory work.

CONCLUSIONS

1. There has not been a successful PMV on Valent's clethodim compound specific method RM-26D-1 as was presented by Valent.

2. The method is remanded to the petitioner for extensive revision as suggested by the ACB PMV report.

3. The petitioner is to have his rewritten clethodim method validated in the laboratory of his choice using the same clethodim and sethoxydim metabolites at the same levels in the same matrices as were used in EPA petition method validation.

4. The petitioner is reminded to provide EPA's Pesticides and Industrial Chemical Repository with a portion of all clethodim reference standards used in the PMV.

5. Valent's clethodim compound specific method, RM-26D-1, is not suitable to gather residue data or enforce tolerances in its present form.

RECOMMENDATION

At this time CBTS recommends that the compound specific method RM-26D-1 for clethodim and sethoxydim **NOT** be forwarded to either FDA's Technical Editing Group for publication in PAM-II or to PIB/FOD for distribution to interested parties.

CBTS could recommend for a tolerance with an expiration date not to exceed 1 year, for total clethodim residues on cottonseed at 1 ppm, in soybeans at 10 ppm, 0.2 ppm in meat, fat, and meat byproducts of livestock and eggs, 0.05 ppm in milk, 15 ppm on soybean soapstock, and 2 ppm in cottonseed meal, if the petitioner agrees to rewrite the compound specific method as suggested by ACB, generate the requested additional validation data, and resubmit this method package for Agency review, and additional testing or revisions as necessary.

CBTS reiterates that once there is a compound specific method that has passed an Agency PMV with acceptable independent laboratory validation, then CBTS could recommend for a permanent set of clethodim tolerances, and both methods, i.e., the common moiety and compound specific method, will forwarded to FDA and PIB/FOD.

cc: R.F., Circ (7), Reviewer(FDG), PP# 9F3743, R.F.Thompson (Repository-MATRICES-NC), Clethodim Subject File, TOX, FDA (Corneliussen, HFF-426), M.Bradley (PAM-II Coeditor/MTO File), D. Hill (OCM-NEIC-Denver), H. Hundley (ACB-Beltsville), PIB/FOD (Furlow).

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