Please return to V. Tarlow Rm. 242

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

APR 17 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 9F 3743 - Clethodim (Select®) in/or Soybeans, Cottonseed, and Animal Commodities.
Review of March 6 and 15, 1991 Amendments.
(No MRID #) [DEB # 7739 and 7769]
(HED Project # 1-0796 and 1-0864)

FROM: Francis D. Griffith, Jr., Chemist
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Francis D. Griffith

THRU: Richard D. Schmitt Ph.D., Chief
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TO: Joanne J. Miller, PM-23
Fungicide-Herbicide Branch
Registration Division (H-7505C)

Valent U.S.A. Corporation has submitted these amendments consisting of two cover letters. Neither letter directly addresses the deficiencies noted in our March 12, 1991 review by F.D. Griffith, Jr., (which see). The March 6, 1991 letter, signed by Patricia B. Pomidor, Project Manager discusses residue data generated by Craven Laboratories. The March 15, 1991 letter, signed Richard H. Stanton, Federal Registration and Regulatory Affairs manager, requests a conditional registration of Select® if the primary method PMV (petition method validation) is successful, but prior to the completion of the PMV on the confirmatory analytical method (specific method). CBTS will comment on each letter in the sequence of letter dates. Our conclusions and recommendations follow.

EXECUTIVE SUMMARY OF CHEMISTRY DEFICIENCIES

- Successfully complete Petition Method Validations (PMVs) on the proposed enforcement method and confirmatory residue analytical method.

CONCLUSIONS

1. CBTS Conclusions on **Residue Analytical Methods**

a. CBTS has previously requested ACB/BEAD conduct a new PMV on the revised version of Analytical Method RM-26B-2 (MRID # 416234-01), the proposed primary common moiety enforcement method (see memorandum by F.D. Griffith, Jr., to D.A. Marlow on October 23, 1990). CBTS continues to defer judgement on the method being an enforcement method pending review of a new ACB/BEAD PMV report. The deficiency remains unresolved and continues outstanding.

b. The petitioner has submitted a quantity of the interval standard or marker compound, cloproxydim sulfoxide (reference grade) along with supporting documentation. Although some questions remain on the adequacy of the Material Safety Data Sheet (MSDS), CB will not consider this to be a deficiency for the time being. CB points out if this compound is not available for distribution to enforcement labs by the completion of the PMV this may become a deficiency that could prevent a favorable recommendation for a clethodim tolerance. Judgement is now deferred on whether or not the deficiency is resolved.

c. The use of method validation data generated by Craven Laboratories is not an issue. CBTS has adequate multi-year method validation data generated by Chevron to show the method is suitable together crop field trial residue data. Acceptability of the revised method rests on other criteria than Craven method validation data; eg, Chevron's recovery data and the results of the PMV.

d. The PMV requested for the revised Analytical Method EPA-RM-26D-1 (MRID # 413707-01), the proposed compound specific confirmatory method can not be completed as requested due to lack of sufficient method validation data for clethodim and sethoxydim, parent and/or selected metabolites at various levels. For those portions of the PMV which we have adequate method validation on hand, the PMV will continue. The ACB lab is to continue its efforts to obtain the proper HPLC columns and analytical reference standards prior to starting the PMV.

The petitioner is expected to provide an adequately written method and additional method validation data for clethodim and its metabolites and sethoxydim and its corresponding metabolites to show that the method will be qualitative, reasonably quantitative, and can distinguish between these compounds in tolerance enforcement. The deficiency remains unresolved and continues outstanding.

2. CB Conclusion on **Product Chemistry**

The deficiencies associated with the product chemistry of clethodim have been resolved in a copending action to this petition.

3. CB Conclusion on **Magnitude of the Residue-Crop Field Trials**

a. After careful reconsideration CB no longer considers the 1986 crop field trial clethodim residue data for soybeans and cottonseed to be relevant in determining the magnitude of the residue. These studies have residue data generated by Craven Laboratories. The studies presented data for DME only derived residues. Since the petitioner proposes that the clethodim tolerances be expressed as DME + DME-OH, the 1986 soybean and cottonseed trials are not relevant with DME only data. Nor will we continue to accept them as supplementary.

b. CB has additional adequate multi-year geographically representative soybean crop field trial data that shows residues of clethodim and its metabolites are not expected to exceed the proposed tolerance of 10 ppm from the proposed directions for use of Select® Herbicide.

c. CB has additional adequate multi-year geographically representative cottonseed crop field trial data that shows residues of clethodim and its metabolites are not expected to exceed the proposed tolerance of 1 ppm from the proposed directions for use of Select® Herbicide.

4. CB Conclusion on **Proposed Tolerances**

a. CB reiterates that judgement on the adequacy of the proposed tolerances is deferred until there have been successful PMVs. CB tentatively concludes that residues of total clethodim are not expected to exceed the proposed tolerances from the proposed conditions of use of Select® Herbicide. This deficiency is not resolved and continues outstanding.

b. After reviewing Valent's rationale for granting of a conditional registration, CB feels it is prudent not to grant a conditional registration and thus tolerances. While granting of a conditional registration is a prerogative of the Registration Division, CB notes there are no residue analytical methods suitable to properly enforce tolerances, or confirm total clethodim residue levels, if they should be detected.

RECOMMENDATION

At this time CB recommends against the establishment of the proposed clethodim plus its metabolites containing the 2-cyclohexene-1-one moiety tolerance in or on the commodities of this petition for reasons cited in our Executive Summary and further explained in our Conclusions 1a, 1d, and 4 above.

For further considerations of the proposed tolerance, the petitioner should be advised to resolve the deficiencies noted above.

DETAILED CONSIDERATIONS

MAGNITUDE OF THE RESIDUE - CROP FIELD TRIALS

Valent's March 6, 1991 Letter

In the letter Valent acknowledges that the crop field trial residue data in two 1986 studies were generated by Craven Laboratories. These two studies are:

1) MRID # 410302-15, "Magnitude of Clethodim Residues in Cotton - 1986"

2) MRID # 410302-18, "Magnitude of Clethodim Residues in Soybeans - 1986".

On page 2 of the letter the petitioner states that "The residue analytical methodology used at Craven was developed by Chevron Chemical Company and has been validated by Chevron and a number of other contract laboratories since 1986 including Analytical Development Corporation and EPL Bio-Analytical Services, Inc. Also, EPA is in the final stages of completing its own petition method validation (PMV) of this methodology, also known as the common moiety method." The letter does not identify all of the Craven clethodim method validation data. This paragraph should have referenced Craven method validation data that was part of the same petition submission. Valent omitted saying that Craven generated their own method validation data which are included in MRID # 410301-41. This MRID number was not included in Valent's March 6 response and it should have been. CBTS notes additional Craven analytical method validation (or recovery) data that are presented in MRID #410301-41 "Analytical Method or the Determination of Clethodim Residues", RM-26 are on pages 9 and 19. It very clearly states on page 9 that "The method was first validated for clethodim and its major metabolite/degradate, clethodim sulfoxide in cotton and soybean. The results obtained by Craven Laboratories are summarized in Table III". The title of Table III on page 19 is "Validation of

Clethodim Sulfoxide in Cotton and Soybeans by Craven Laboratories"

In response to an inquiry from PM-23 and the Fungicide-Herbicide Branch Chief CBTS feels the March 6, Valent letter does NOT indicate that Craven Laboratories did their own method validation for the 1986 studied. In general all labs generate their own method validation data as a normal operation prior to sample analysis. CB hastens to point out the method validation data generated by Craven Labs is not to be considered the second laboratory validation of the method. No second lab validation as such was presented for method RM-26 or RM-26A-1 as the study was completed prior to the time the second lab validation requirement went into effect. As far as CBTS is concerned we are satisfied that the facts show Craven Labs did their own method validation as would have been expected. Had no method validation data been presented with the 1986 crop field trials these magnitude of the residue data would not have been considered relevant in determining the proper tolerance level.

Also the question arose as to how did ACB/BEAD knew that Craven Labs generated method validation data. As part of any PMV request CB provides the lab in ACB with not only a step wise procedure but also all recovery data and chromatograms presented whether it is in the method study, storage stability studies, crop field trials, and/or feeding studies. In this instance the PMV was requested for method RM-26B-1; thus, method RM-26A-1 with its validation would at some point be sent to the lab as additional validation data. In summary the ACB lab in Beltsville knew Craven Labs generated the initial method validation data because CB sent ACB the Craven information.

The petitioner is correct that on page 21 of our Residue Chemistry review of March 12, 1990, (by M.J.Nelson) that CB considered the 1986 cottonseed and soybean clethodim crop field trial residue data are supplementary. After careful reconsidation CB concludes the 1986 crop field trial clethodim residue data on soybeans or cottonseed are not adequate. The reason is that the data presented are for the DME residues from compounds that will form DME. Since the petitioner proposes tolerances that include metabolites determined as DME + DME-OH, these data from crop trials for DME are not complete; thus they are no longer considered relevant.

CB has additional adequate multi-year geographically representative soybean crop field trial data that shows residues of clethodim and its metabolites are not expected to exceed the proposed tolerance of 10 ppm from the proposed directions for use of Select® Herbicide.

CB has additional adequate multi-year geographically representative cottonseed crop field trial data that shows residues of clethodim and its metabolites are not expected to

exceed the proposed tolerance of 1.0 ppm from the proposed directions for use of Select® Herbicides.

The Craven studies did not present residue data for DME-OH derived residues; thus, we will not consider them further for deciding on an appropriate tolerance.

PROPOSED TOLERANCES

Valent's March 15, 1991 Letter

The petitioner is requesting a conditional registration of Select® Herbicide, if and when the common moiety analytical residue method completes the PMV requested by CBTS in October 23, 1990. The granting of a conditional registration (and thus tolerances) is the prerogative of the Registration Division.

Valent offers various reasons for the granting of a conditional registration. After reviewing Valent's rationale CB feels it would be prudent not to grant a conditional registration.

Valent contends the PMV request of February 22, 1991 is a new data requirement. CB points out that in our October 23, 1990, PMV request for validation of the common moiety method CB clearly states on page 2 paragraph 4 "... for the confirmatory method RM-26D-1 ... DEB plans to initiate a separate PMV request." In our amendment reviews of November 19, 1990, December 13, 1990, and March 12, 1990, in the Executive Summary of Chemistry Deficiencies, we clearly state "Run a Petition Method Validation (PMV) on the Proposed enforcement and the confirmatory method." Going back to the initial review of March 12, 1990, on page 18 we clearly alerted the petitioner we were planning on a PMV for this confirmatory method once it was presented in an adequate format and with sufficient method validation data for initiating a PMV. The petitioner's argument that the confirmatory PMV is a new data requirement is without merit.

The petitioner contends that once the common moiety method RM-26B-2 completes its PMV it will be adequate to detect tolerance violations and protect human health. CB does not agree.

CB reiterates the Agency needs to have adequate analytical enforcement methods for clethodim that can separate clethodim and its metabolites from sethoxydim and its metabolites. CB points out that the established sethoxydim tolerances in 40 CFR 180.412 are 5 ppm for cottonseed and 2 ppm in eggs. The proposed clethodim tolerances are 1 ppm in cottonseed and 0.2 ppm in eggs. Thus, it is imperative for enforcement agencies to have a proven confirmatory or compound specific procedure that is qualitative,

reasonably quantitative, and can distinguish between sethoxydim and clethodim in eggs between 0.2 ppm and 2 ppm, and in cottonseed between 1 ppm and 5 ppm. To put the problem in a slightly different perspective, if a regulatory chemist using method RM-26B-2 found 2 ppm in cottonseed or 1 ppm in eggs, then no regulatory action can be initiate without a validated method such as EPA-RM-26D-1 to separate sethoxydim (no action initiated) from clethodim (regulatory action required).

Method EPA-RM-26D-1, the specific compound method is a controlled oxidative HPLC procedure that is designed to measure five separate analytical entities which are clethodim/sulfoxide/sulfone, sethoxydim/sulfoxide/sulfone, 5-hydroxyclethodim sulfoxide/sulfone, 5-hydroxysethoxydim sulfoxide/sulfone, and S-methylclethodim sulfoxide. Common moiety method RM-26-B-2 is a total oxidation GC method that will also determine all of these compounds but only as DME, DME-OH, and S-MeDME: no separation of clethodim from sethoxydim. Based on ^{14}C-clethodim studies we know that clethodim sulfoxide and clethodim sulfone along with their respective 5-hydroxy derivatives are present in soybeans, cottonseed and cotton foliage. From ^{14}C-clethodim livestock metabolism studies we know that clethodim, per se, clethodim sulfoxide and clethodim sulfone are present in ruminant tissues; ie, liver, kidney, heart, fat and in milk, and in poultry tissues; ie, kidney, liver, skin, fat, gizzard and in eggs. The S-methyl clethodim sulfoxide is present only in ruminant tissues and milk. From ruminant and poultry feeding studies where residue data were gathered using method RM-26A (or RM-26A-1) residues of DME and S-Me-DME were detected in the same tissues as were detected in the corresponding metabolism study. Again, in cases of over tolerance residues whether or not from overt misuse of either herbicide the Agency needs a valid method that can distinguish clethodim from sethoxydim.

CB reiterates that the petitioner is expected to provide the requested additional performance and recovery data for method EPA-RM-26D-1 as discussed in the EPA-Valent April 9, 1991 meeting. The petitioner is expected to define the analytical limit of detection (as opposed to a limit of sensitivity or quantification) for method EPA-RM-26D-1 in the matrices for the PMV. As a result of this meeting CBTS plans to initiate a modified PMV that is reduced in scope for the number of compounds and levels to be confirmed. While the metabolites and their fortification levels to be in the amended PMV will depend on the data presented by Valent it is our intend to modify the compound specific PMV along the lines discussed in our April 9 meeting. Our request for sethoxydim and its metabolites method validation data thru method EPA-RM-26D-1 is not to validate the method for enforcement of sethoxydim tolerances. Rather it is to prove that if residues of sethoxydim and its metabolites were present in samples that contained clethodim and its metabolites, then

sethoxydim residues would not interfere with the identification and quantitation of clethodim.

The petitioner should review the CBTS memorandum of April , 1991 on the ACB reports of the pretrial review of method RM-26D-1 for details on the amount of additional method validation that needs to be submitted before the Agency PMV on this method can proceed to completion. For the compound specific method quantification of recoveries is still necessary for those metabolites of clethodim and sethoxydim and at the levels agreed to in our meeting. However, these recoveries need not in all cases be 70% or greater. The Agency has the common moiety method that will adequately quantitate residues of total clethodim for enforcement purposes. It is intended that the compound specific confirmatory method serve as a check on the common moiety method to be sure all of the residues detected are in fact clethodim.

Select® and Post® may rarely be used on the same fields. None-the-less the possible use of both herbicides on the same field can and probably will happen. Valid analytical residue enforcement methods need to be in place before this happens. CB notes that there are no deficiencies in the directions for use of Select. However, if the petitioner wishes to change the label to add a restriction from using both Select® and Poast® on the same fields within the same crop growing season, CB will be glad to review and comment on such a proposal.

CB reiterates we can not complete the compound specific confirmatory PMV on method EPA-RM-26D-1 due to insufficient method validation data. We agree with the petitioner that the PMV for method EPA-RM-26D-1 can not be completed before spring planting of the crops in the petition and in light of the additional validation data needed it probably will not be completed prior to the 1991 normal harvest for both soybeans and cotton.

CB makes no comments on the petitioner's claim that only 300,000 acres would be with clethodim this year.

CB reiterates that judgement on the adequacy of these propose tolerances is deferred until there have been successful PMV's.

H-7509C:Reviewer(FDG):vg:CM#2:RM814B:557-0826

cc: RF., Circu(7), Reviewer (FDG), PP#9F3743 Clethodim Reg. Std. File, TOX, D.A.Marlow, Chief ACB/BEAD, H.K.Hundley - Beltsville Lab, R.D. Schmitt, Ph.D., Chief

RDI:SecHd:RSQuick:4/12/91:BrSrSci:RALoranger:4/12/91.