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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

CERTIFIED MAIL

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SUBJECT: Nature of the residue studies for rice and peanuts for reregistration of sodium acifluorfen, chemical code 114402

Dear Ms. Blundell:

This letter is in response to your June 22, 1992 submission of data for guideline requirement 171-4(a), nature of the residue in peanuts and rice, for the reregistration of sodium acifluorfen. We have reviewed these data, MRID 423683-01 and 423683-02, and they are upgradable with the submission of additional data.

Metabolism in Peanuts: The qualitative nature of sodium acifluorfen in peanuts is not adequately understood because MRID 423683-01 failed to identify the majority of ^{14}C residues in samples of peanut commodities that were collected at maturity. This study may be upgraded if you can address the specific issues and requirements listed below:

1. In reporting radioactivity in each fraction, you must also report the initial sample TRR, allowing losses during extraction to be determined.

2. Non-extractable residues remaining after acid hydrolysis represent barely 10% of TRR in vines, and smaller percentages in hulls and kernels. No further work is required to release the remaining non-extractable residues.

3. Because HPLC System II was used to confirm the identity of metabolites, representative chromatograms from the confirmatory analysis must be provided.

4. The data provided indicate that metabolism is extensive, and little acifluorfen is found, in mature peanut commodities. However, the data are insufficient to identify the metabolites present in mature commodities; less than 1% of TRR in kernels, 10% of TRR in hulls, and 16% of TRR in vines have been

identified. Unidentified polar metabolites in the organic fraction from the ACN:HCI extraction account for up to 43.3% of TRR (0.370 ppm) in vines, and 39.2% of TRR (0.404 ppm) in hulls.

5. Because of the small magnitudes of individual chromatographic peaks, further characterization of residues in peanut kernels is not required. In mature hulls and vines, each individual metabolite ≥10% of TRR should be identified. Residues extracted by either or both of the ACN:HCI method and the Bligh-Dyer method may be used for identification, but the overall tabulation of identified residues must be reconciled between the two extracts (that is, "double-counting" the same metabolite from both extracts is not allowed). Identification or characterization of residues should be consistent with Additional Guidance for Conducting Plant and Livestock Metabolism Studies, D. Edwards and E. Zager, 7/16/92, a copy of which is attached to the review.

6. You have proposed that the metabolism of ^{14}C sodium acifluorfen in peanut plants proceeds by conversion of the parent compound to form polar and acidic conjugates, reduction and cleavage of the nitro group, decarboxylation, and cleavage of the diphenyl ether bond. You also believe that ^{14}C fractions are incorporated into insoluble plant materials. Because polar metabolites and/or conjugates have not been identified, and evidence for incorporation into plant components has not been provided, the proposed metabolism scheme cannot be considered justified. You must provide evidence of this scenario.

7. Storage times and conditions at the analytical laboratory must be provided. If storage times were greater than six months between harvest and analysis, evidence should be provided that the profile of residues did not change during the period between collection and final analysis.

8. Radiovalidation of method(s) using samples from the metabolism study remains an outstanding requirement, pending determination of the residues to be regulated.

Metabolism in Rice: The qualitative nature of the residue in rice is not adequately understood because complete quantitative data pertaining to metabolite identification were not submitted; the results of metabolite identification in rice straw were described by you in narrative text. It may be possible to upgrade the study if you can address the specific issues and requirements listed below:

1. You must resolve the discrepancies in the reported HPLC retention times for reference standards of acifluorfen and amino-acifluorfen versus. the reported retention time for acifluorfen in rice samples. This discrepancy could be resolved by the submission of HPLC profiles of reference

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compounds recorded on the same day as the analysis of metabolites.

2. Samples were collected at 97 days, while samples at the minimum PHI of 50 days might have contained greater TRR. Considering that acifluorfen is still present in the 97 day samples, metabolism would be expected to be more extensive than at the minimum PHI. The samples at 97 days may therefore be acceptable, provided identification of residues is adequate.

3. You must explain in more detail how quantitative assignment of residues in rice grain was made. Assignments should be supported by calculations and data on radioactivity applied to TLC plates and recovered.

4. Organosoluble residues from hulls should be examined for the putative acifluorfen peak; identification of acifluorfen by two methods in hull extracts could be translated to grain.

5. For each identified metabolite (whether tentative or confirmed) in rice straw, complete quantitative data must be provided. These data should be presented in a table which must include the amount (% of TRR and ppm equivalents) for each extractable fraction of rice straw. The amount (% of TRR and ppm equivalents) of unidentified polar metabolites should also be provided. Further characterization or identification of residues should be conducted based on Additional Guidance for Conducting Plant and Livestock Metabolism Studies (enclosed). Cleavage by appropriate enzymes should facilitate identification of putative conjugates.

6. You proposed that ^{14}C sodium acifluorfen is metabolized in rice by two pathways: a route involving formation of amino acifluorfen by the reduction of nitro group; and a route involving rapid cleavage of the diphenyl ether bond. Only two metabolites, acifluorfen and amino-acifluorfen, were identified in rice commodities, and the identification of acifluorfen was confirmed only in straw. The proposed metabolic route involving cleavage of the diphenyl ether bond cannot be considered justified until putative conjugated metabolites are identified.

7. The data presented are insufficient to validate the stability during frozen storage of organosoluble residues in grain, nor aqueous soluble residues in straw. Storage conditions between harvest and homogenization should be provided for grain and straw. Considering the very long storage times, evidence should be provided that the profiles of radioactive residues did not change during storage. If chromatographic profiles at early extraction are not available, then material balances indicating that residue identification and quantitation

account for nearly all residues at early extraction will be sufficient evidence for storage stability.

8. Radiovalidation of method(s) using samples from the metabolism study remains an outstanding data requirement, pending determination of the residues to be regulated.

RECOMMENDATIONS

Further work is necessary to resolve the deficiencies identified above. Copies of our reviews are enclosed. If it proves necessary to conduct a new metabolism study in rice, the nature of the residue in grain and straw at a PHI of 50 days should be determined; exaggerated rates may be necessary to generate TRRs large enough for adequate identification. The results of the present study can be used as guidance on which compounds would be likely metabolites.

A copy of Additional Guidance for Conducting Plant and Livestock Metabolism Studies, D. Edwards and E. Zager (7/16/92), is provided as an attachment to this review. You should consult this document for guidance on the extent to which further characterization/identification of unidentified metabolites should be conducted. However, you must also recognize that the goal of a metabolism study is identification of the chemical components of the residue.

You must provide the additional information necessary to upgrade these two studies by July 31, 1993. If you do not provide these data within the provided time frame, we may pursue appropriate regulatory action to ensure your compliance with our statutory goals. If you have any questions regarding this letter, please call the Chemical Review Manager, Tom Luminello in the Accelerated Reregistration Branch at (703) 308-8075.

Sincerely yours,

Jay S. Ellenberger, Chief
Accelerated Reregistration Branch
Special Review and
Reregistration Division

Enclosure

cc: Joanne Miller, PM-23
Steven Knizner, HED