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

OCT 13 1988

EXPEDITE

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#7F3476/FAP#7H5524. Myclobutanil (RALLY) in or on Apples, Grapes, Their Byproducts, Meat, Milk, and Eggs.

Amendments of 8/12/88 and 9/16/88.

DEB Nos.: 4378-4384; 4412-4413.
MRID Nos.: 408033-01 thru -04; 408253-01.
HED Project #: 8-1205; 8-1248.

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mjn

THRU: Charles L. Trichilo, Ph.D., Chief
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Toxicology Branch - HFA Support
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Science Analysis & Coordination Branch
Health Effects Division (TS-769C)

This review is being EXPEDITED at the request of the Registration Division (9/28/88 memo of E. F. Tinsworth, Acting Director). The due date for its completion is 10/14/88.

Myclobutanil is a new chemical, and this petition proposes the first food-use permanent tolerances.

DEB's initial review of this petition (dated 2/8/88) was formatted to serve as a Registration Standard for Myclobutanil. This current review is in DEB's normal petition amendment format.

Once the remaining deficiencies have been resolved, a revised version of the residue chemistry "chapter" of the Registration Standard for Myclobutanil will be prepared. That document will be accompanied by a Table A (Generic Data Requirements).

SUMMARY OF DEFICIENCIES REMAINING TO BE RESOLVED FOR DEB

- A revised Section F is needed.
- The PMV for RH-9090 (bound)/milk must be completed, and that method accepted by DEB as suitable for regulatory purposes.
- A final decision on the adequacy of the proposed tolerance level for milk is deferred until the results of the PMV for RH-9090 (bound)/milk are received and evaluated.

CONCLUSIONS

- > 1. A revised Section F has been submitted, but it needs to be further revised to:
 - o Propose the tolerance level in liver at 0.3 ppm;
 - o Replace reference to 21 CFR 193 with 40 CFR 185;
 - o Replace reference to 21 CFR 561 with 40 CFR 186; and,
 - o Specify the pomace proposals in terms of "Apple pomace (wet and dry)" and "Grape pomace (wet and dry)".
- 2a. The proposed tolerance levels on all the commodities of this petition (except for milk) are appropriate (assuming the liver tolerance is proposed at 0.3 ppm), and can be adequately enforced by the analytical methods which have undergone PMV.
- > 2b. Final judgment on the adequacy of the proposed tolerance level of 0.05 ppm for milk is deferred pending receipt and review of the PMV results for RH-9090 (bound) in milk.
- 3a. Satisfactory enforcement methods are now available for all the regulable residues and commodities of this petition, with the exception of RH-9090 (bound)/milk.

We can also conclude these methods were adequate for generating the residue data for this petition.
- > 3b. Judgment on the adequacy of the RH-9090 (bound)/milk method for generating residue data and for enforcing the proposed tolerance on milk is deferred, pending receipt and evaluation of the PMV report.
- 4. All the components of the regulable residue have now been tested through the FDA PAM I multiresidue protocols (except bound RH-9090, which is not applicable since it hydrolyzes to free RH-9090, which was tested).

5. The raw data from the processing of apples from crop field trial 84-0238 have been submitted, as requested.
- 6a. We can now conclude the submitted apple field trial and processing study data were generated by analytical methodology adequate for that purpose and for enforcing the proposed tolerances on those commodities.
- 6b. We can now conclude the submitted grape field trial and processing study data were generated by analytical methodology adequate for that purpose and for enforcing the proposed tolerances on those commodities.
7. Tolerance Assessment System (TAS) considerations are now under the purview of the Special Analysis & Outreach Section (SAOS) of the Science Analysis and Coordination Branch (SACB), HED.

At such time as DEB is able to make a favorable recommendation for the establishment of the tolerances proposed by this petition, a copy of that DEB review will be routed to SAOS/SACB/ HED for their use in preparing any TAS assessment which may be required.

RECOMMENDATIONS

DEB continues to recommend against the establishment of the proposed tolerances of this petition for the reasons cited in Conclusions 1, 2b, and 3b.

For further consideration of this petition, Rohm and Haas should submit a suitably revised Section F.

PM, PLEASE NOTE our comment under Conclusion 7.

DETAILED CONSIDERATIONS

INTRODUCTION

By transmittal letter dated 8/12/88, the petitioner (Rohm and Haas Company (RH)) has submitted a response to the deficiencies cited in our (M. Nelson) review of 4/26/88.

The response consists of a revised Section F, two revised analytical methods, multiresidue screen results for RH-0294 (diol metabolite), raw data from an apple processing study (RAR 84-0238), and point-by-point comments.

By transmittal letter dated 9/16/88, the petitioner has submitted a response to the deficiency cited in our (M. Nelson) method validation review of 7/27/88.

The response consists of a revised analytical method for free RH-9090 (alcohol metabolite) in meat, milk, and eggs.

This review will cover the deficiencies outstanding from our 4/26/88 amendment review and our analytical method validation (PMV) reviews of 4/12/88, 4/14/88, and 7/27/88; the responses by RH; and, DEB comments/conclusions.

DEFICIENCY: Proposed Tolerances

DEB: A revised Section F is needed.

RH: A revised Section F is submitted, incorporating DEB recommendations.

DEB: RH's revised Section F (dated 8/12/88) is in compliance with our request (4/26/88 review), except that 0.03 ppm is erroneously being proposed for liver when it should be 0.3 ppm.

----> We assume this is a typo, but the petitioner is requested to submit another Section F which corrects the tolerance level proposal for liver to 0.3 ppm.

----> Since pesticide food and feed additive regulations have recently (53 FR 24666, 6/29/88) been redesignated from 21 CFR Parts 193 and 561 to new Parts 185 and 186 in 40 CFR, RH should also incorporate these changes in the revised Section F.

----> We also request the revised Section F designate the pomace proposals as "apple pomace (wet and dry)" and "grape pomace (wet and dry)" for consistency with current policy.

This deficiency is not yet satisfactorily resolved.

DEB: Final judgment re the appropriate levels of tolerance is deferred until PMVs of the proposed enforcement methods for the various components of the regulable residue in the commodities of this petition verify adequate levels of recovery and sensitivity at (or below) the suggested tolerance levels.

RH: A revised Section F is submitted, proposing the tolerance levels the Agency suggested as appropriate for the commodities of this petition.

DEB: As discussed above, RH is now (inadvertently) proposing an incorrect tolerance level (0.03 ppm) for liver and this needs to be corrected to 0.3 ppm via a further revised Section F.

We have not yet received from ACB/BEAD the results of the PMV for RH-9090 (bound) in milk.

Three of the other four analytical methods (for parent + RH-9090 (free and bound) in crops; RH-9090 (free) in meat, milk, poultry, and eggs; and, RH-0294 (diol) in milk) have all undergone PMV with satisfactory levels of recovery and sensitivity. (See M. Nelson memos of 4/14/88, 7/26/88, and 7/27/88.)

The analytical method for parent in meat, milk, poultry, and eggs underwent a troublesome PMV with low recoveries, which ACB/BEAD overcame by a slight modification to the analytical procedure (see 4/12/88 memo of M. Nelson). RH has now explained (MAM 88-69, 8/12/88) this difficulty was due to a typographical error in the written method re the concentration of the eluting solvent during Florisil column clean-up.

The rewritten version of the parent/meat, milk, poultry, eggs method (MRID# 408033-01) corrects the typo and incorporates the previously separate addendum 310-86-09.

RH also explains no other changes to the method were made since the corrected version is reflective of the validation and data generation carried out in their labs, and is very similar to the modification independently conceived by the Agency to compensate for the poor recoveries.

DEB accepts the RH explanation and the validation data which accompanies the method (all in MRID# 408033-01).

RH reports the sensitivity of the parent/meat, milk method to be 0.005 ppm for determining parent in animal commodities (meat, milk, eggs). Recoveries of parent from eggs and bovine liver, kidney, fat, muscle, and milk fortified at 0.01-0.05 ppm ranged 68-103% (n=16). Representative controls (chromatograms) indicated no detectable residue.

The deficiencies cited in our (M. Nelson) PMV review of 4/12/88 are now considered to have been adequately addressed by RH, and this method (parent/meat, milk) is now considered to be acceptable for enforcement purposes.

----> Final judgment on the adequacy of the proposed tolerance level of 0.05 ppm for milk is deferred pending review of the PMV results for RH-9090 (bound) in milk.

We can conclude the tolerance proposals on the other commodities of this petition can be adequately enforced by the pertinent analytical methodology.

This deficiency is not yet completely resolved.

DEFICIENCY: Residue Analytical Methods

DEB: Final judgment on the adequacy of the analytical methods for measuring residues and for enforcement is withheld pending completion of PMVs and any necessary revisions required to make the methods acceptable for regulatory purposes.

RH: Appropriate revisions have been made to the analytical methods, as requested.

DEB: PMVs of five different analytical methods have been necessary in conjunction with the proposed tolerances.

Four of those PMVs have been completed to date, and evaluated by DEB (see M. Nelson memos of 4/12/88, 4/14/88, 7/26/88, and 7/27/88).

PMV indicated one of those four analytical methods (RH-0294/milk; Rpt 31S-87-02, MRID# 404813-01) was adequate, as written.

The other three analytical methods required very minor revisions by RH, which have now been satisfactorily accomplished.

These revised methods are coded Rpt 34S-88-21 (MRID# 408033-01; PMV'd for parent/meat, milk); Rpt 34S-88-10 (MRID# 408033-02; PMV'd for parent + RH-9090 (free and bound)/apples); and, Rpt 34S-88-22 (MRID# 408253-01; PMV'd for free RH-9090/meat, milk).

DEB can now conclude these four analytical methods are adequate for generating residue data and for enforcing the proposed tolerances of this petition.

DEB has not yet received a report from ACB/BEAD of the PMV of the fifth analytical method (bound RH-9090/milk).

---> DEB defers judgment on the adequacy of the bound RH-9090/milk method for generating residue data and for enforcing the proposed tolerance on milk, pending evaluation of the PMV report by DEB and any method rewrite by RH which might be needed.

This deficiency is not yet totally resolved.

DEB: An enforcement method is needed for RH-9090 (bound) in milk.

RH: "Bound RH-9090 Residue Analytical Method for Milk", Rpt 34S-88-15, was submitted 6/3/88.

DEB: That report has been assigned MRID# 406458-01.

PMV was requested of ACB/BEAD by DEB on 6/22/88. The PMV was delayed awaiting receipt from RH of a bound RH-9090 standard. A PMV report from ACB/BEAD has not yet been received by DEB.

---> The results of the PMV are needed before we can determine if RH has submitted an acceptable enforcement method. In the interim, this deficiency remains outstanding.

DEB: RH-0294 needs to be tested through the applicable FDA multiresidue protocols.

RH: RH Rpt. 34A-88-39, "FDA Multiresidue Screen Results for RH-0294", is herewith submitted.

DEB: That report, dated 8/5/88, has been assigned MRID# 408033-03. RH-0294 was tested through Protocols I-IV and found not to be amenable to the multiresidue methodology. DEB will transmit this report to FDA for the future updating of PAM I.

This deficiency is resolved.

DEFICIENCY: Magnitude of the Residue - Apples

DEB: The raw data from the processing of apples from crop field trial 84-0238 should be submitted, if available.

RH: The requested data are submitted as Rpt 34S-88-19.

DEB: The report has been assigned MRID# 408033-04.

This deficiency is resolved.

DEB: Final judgment re the adequacy of submitted apple field trial and processing study data is deferred until the PMV is completed and evaluated.

RH: Rpt 34S-88-10 (MRID# 408033-02) is the total residue analytical method for measuring parent and RH-9090 (free and bound) in apples and grapes, as revised to correct the typo in concentration of eluting solvent and to incorporate its previously separate addendum (310-86-09). This method is very similar to the modification developed by ACB/BEAD to achieve adequate recoveries during the PMV.

DEB: Based on RH validation data which accompany this analytical method (see MRID# 408033-02; also see discussion on page 5 of this review), we can now conclude the submitted apple field trial and processing study data were generated by analytical methodology adequate for that purpose.

This deficiency is resolved.

DEFICIENCY: Magnitude of the Residue - Grapes

DEB: Final judgment re the adequacy of submitted grape field trial and processing study data is deferred until the PMV is completed and evaluated.

RH: See above, under Apples.

DEB: See above, under Apples.

We can now conclude the submitted grape field trial and processing study data were generated by analytical methodology adequate for that purpose.

This deficiency is resolved.

OTHER CONSIDERATIONS

Tolerance Assessment System (TAS): These considerations are now under the purview of the Special Analysis & Outreach Section (SAOS) of the Science Analysis and Coordination Branch (SACB), HED.

At such time as DEB is able to make a favorable recommendation for the establishment of the tolerances proposed by this petition, a copy of that DEB review will be routed to SAOS/SACB/HED for their use in preparing any TAS assessment which may be required.

cc: M. Nelson
PP#7F3476/FAP#7H5524
Myclobutanil Registration Standard File
Reading File
Circulation (7)
ISB/PMSD (Eldredge)

TS-769C:DEB:Reviewer(MJN):CM#2:Rm804:557-7324:typist(mjn):10/12/88.

RDI:SectionHead:RSQuick:10/12/88:DeputyChief:RDSchmitt:10/12/88.