PMSP/ISB

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

3 NOV 1988

EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#7F3476/FAP#7H5524 and EPA File Symbols 707-ERN, -ERR, -ERE, -ERL, -EER, [redacted]

Myclobutanil (RALLY®) in or on Apples, Grapes, Their Byproducts, Meat, Milk, Poultry, and Eggs.

1) Evaluation of the PMV Report of Bound RH-9090 in Milk; and,
2) Recommendation for the Establishment of Tolerances.

DEB Nos.: 4532-4540.
MRID No.: None.
HED Project #: 8-1205A.

FROM: Maxie Jo Nelson, Ph.D., Chemist
Dietary Exposure Branch
Health Effects Division (TS-769C)

mjn

THRU: Charles L. Trichilo, Ph.D., Chief
Dietary Exposure Branch
Health Effects Division (TS-769C)

TO: L. Rossi/L. Schnaubelt, PM Team 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

Toxicology Branch - HFA Support
Health Effects Division (TS-769C)

Special Analysis & Outreach Section
Science Analysis & Coordination Branch
Health Effects Division (TS-769C)

This review is being EXPEDITED at the request of the Registration Division. The due date for its completion is 11/8/88.

SUMMARY OF DEFICIENCIES REMAINING TO BE RESOLVED FOR DEB

None.

CONCLUSIONS

1. ACB has validated that analytical procedure TR 34S-88-15 (MRID# 406458-01), "Bound RH-9090 Residue Analytical Method for Milk", converts bound RH-9090 to free RH-9090, in which form it is measured by EC-GLC.

2. Since acceptable levels of recovery (74-90%) were obtained by the PMV and within a reasonable timeframe (2 days), DEB can now conclude this analytical method is satisfactory for the gathering of residue data and for regulating residues of bound RH-9090 in milk.

3. For regulatory purposes, spiking with free RH-9090 reference standard is appropriate.

4. The PMV has demonstrated this analytical method is suitably sensitive ($\leq$ 0.005 ppm) vis-a-vis the proposed tolerance of 0.05 ppm for combined residues of parent, RH-9090 (free and bound), and the diol (RH-0294) metabolite in milk.

5. The proposed tolerance level of 0.05 ppm for milk is both adequate and appropriate.

6. Once the tolerances proposed by this petition are established, the methods for enforcing those tolerances will be forwarded to FDA for inclusion in PAM II.

7. DEB has no objection to including the ACB comment, "The molecular weight of RH-9090 glycoside is 466.93 and that of free RH-9090 is 304.78; 0.10 ppm of the glycoside thus yields 0.065 ppm of RH-9090 theoretically", as an end note to the Bound RH-9090 Residue Analytical Method for Milk, TR 34S-88-15, when it is sent to FDA for publication in PAM II.

8. No deficiencies now remain to be resolved for DEB regarding this petition.

9. A copy of this review is being sent to SAOS/SACB for their use in any tolerance assessment evaluation which may be needed at this time.

10. An updated Codex sheet is appended to this review. There are no established international limits for the proposed uses, so the question of compatibility does not arise.

RECOMMENDATIONS

Toxicological considerations permitting, DEB recommends in favor of the establishment of tolerances as proposed in Attachment 1 of this review.

PM, PLEASE NOTE Conclusion 9.

A revised version of the residue chemistry "chapter" of the Registration Standard for Myclobutanil, documenting the data supporting this favorable recommendation, will be forthcoming from DEB. That document will be accompanied by a Table A (Generic Data Requirements).

DETAILED CONSIDERATIONS

BACKGROUND

By memo dated 6/22/88, DEB requested the Analytical Chemistry Branch (ACB), Biological & Economic Analysis Division (BEAD), to conduct a petition method validation (PMV) of RALLY's bound RH-9090 metabolite in milk at 0.05 and 0.10 ppm levels of fortification. The bound RH-9090 metabolite was identified by the petitioner (Rohm & Haas) as RH-9090 glycoside. The company's method, "Bound RH-9090 Residue Analytical Method for Milk", by S.S. Stavinski, C.K. Brackett, and W.O. Spencer, June 1988, Technical Report 34S-88-15, MRID# 406458-01, was to be used for the PMV.

By memo dated 10/17/88 (received in HED, 10/25/88), ACB has sent to DEB a report on their PMV.

METHOD SUMMARY

(This method is a modification for milk of the "Total Residue Analytical Method for Apple and Grape", TR 310-84-27, Addendum 31S-87-46, which itself has undergone PMV in re this petition.)

Milk samples are refluxed $\geq$ 6 hours with 0.5N HCl/MeOH. The reflux converts bound RH-9090 residues to free RH-9090. The extract is purified by a petroleum ether partition, two methylene chloride partitions, Chelex 100-Fe^{+++} affinity chromatography, and Bio-Sil A column chromatography. RH-9090 quantitation is via GLC on a Supelco Sup-Herb Megabore column with an EC detector.

Under the operating conditions of the PMV, the retention time of RH-9090 was 6.1 minutes and (based on the chromatograms supplied by ACB) the limit of detection was $\leq$ 0.005 ppm.

PMV RESULTS

Commodity	Spike Added	PPM Added	PPM Found	Percent Recovery
Milk	Bound	0.00	0.005	--
"	RH-9090	0.00	0.005	--
"	"	0.05	0.045	90
"	"	0.05	0.038	76
"	"	0.10	0.078	78
"	"	0.10	0.074	74

ACB COMMENTS

1. The molecular weight of RH-9090 glycoside is 466.93 and that of free RH-9090 is 304.78; 0.10 ppm of the glycoside thus yields 0.065 ppm of RH-9090 theoretically. This information should be included in the method.

2. It takes 2 days to analyze a set of 6 samples.

3. No modifications were made to the method or to the instrument parameters; there were no special precautions to be taken; no procedural difficulties were encountered.

4. The RH-9090 glycoside standard is only 44% pure and very hygroscopic. It is not of acceptable quality for use by regulatory laboratories.

DEB COMMENTS

1. ACB has obtained satisfactory levels of recovery in this PMV from spiking with the bound RH-9090 standard. The ability of the analytical procedure to release bound RH-9090 has thus been adequately validated.

2. The timeframe for analyzing a set of samples (2 days) is within acceptable limits.

3. The limit of detection (based on the chromatograms supplied by ACB of control milk) is $\leq$ 0.005 ppm.

4. ACB has indicated no procedural problems were encountered in running this PMV.

5. ACB has expressed concern re the quality of the RH-9090 glycoside standard for regulatory purposes. However, the purpose of spiking with the bound RH-9090 standard was to verify release of the aglycone by acid hydrolysis and to validate the analytical procedure, which the PMV has done. Henceforth it will be sufficient to spike with free RH-9090, since the PMV has demonstrated this analytical procedure will adequately determine residues of bound RH-9090 in milk, as free RH-9090. An analytical grade (≥98% pure) of free RH-9090 reference standard is available from RTP-NC for enforcement purposes.

6. DEB has no objection to the inclusion of ACB comment #1 as an end note to this procedure when published in PAM II.

7. A copy of this analytical procedure and the PMV report will be sent to FDA for the future updating of PAM II once the proposed tolerances are established. (All the enforcement methods and PMV reports will be sent to FDA at that time.)

OTHER CONSIDERATIONS

Unresolved Issues From DEB Review of 10/25/88: In our review (M. Nelson) of 10/25/88, we withheld a favorable recommendation for the establishment of the proposed tolerances of this petition for the following two reasons:

- 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.

- 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 evaluation of the PMV report.

Based on our evaluation of the PMV report, discussed elsewhere in this present review, we can now conclude: (1) the proposed tolerance level of 0.05 ppm for milk is both adequate and appropriate; and, (2) the bound RH-9090/milk method is adequate for generating residue data and for enforcing the proposed tolerance on milk.

No other deficiencies now remain to be resolved for DEB in re this petition.

International Harmonization: An updated Codex (International Residue Limits) Status sheet is appended to this review as Attachment 2. Since there are no international limits established for these uses, the question of compatibility does not arise in this case.

Tolerance Assessment System Evaluation: A copy of this review will be sent to SAOS/SACB/HED for their use in any tolerance assessment evaluation which may be needed at this time.

ATTACHMENT 1: Listing (dated 8/12/88; coded #0246j/117j; submitted as amendment of 10/7/88) of tolerances to be established and residues to be regulated.

ATTACHMENT 2: Updated International Residue Limits Status sheet (dated 11/2/88).

cc (with Attachments): M. Nelson (DEB)
M. Bradley (DEB)
PP#7F3476/FAP#7H5524
Myclobutanil Registration Standard
Reading File
Circulation (7)

ISB/PMSD (E. Eldredge)
ACB/BEAD (D. Marlow)
FDA (P. Corneliussen, HFF426)
USDA (R. Ellis)

TS-769C:DEB:Reviewer(MJN):CM#2:Rm804:557-7324:typist(mjn):11/2/88.

RDI:SectionHead:RSQuick:11/2/88:DeputyChief:RDSchmitt:11/2/88.

ROHM AND HAAS COMPANY
INDEPENDENCE MALL WEST
PHILADELPHIA, PENNSYLVANIA 19105

ATTACHMENT #1

Based on the data presented in this petition, permanent tolerances are proposed for residues of the fungicide alpha-butyl-alpha-(4-chlorophenyl) -1H-1,2,4-triazole-1-propanenitrile and its metabolites containing both the chlorophenyl and triazole rings as follows:

For 40 CFR 180.XXX:

a. Tolerances for combined residues of RH-3866 and its metabolite RH-9090 (free and bound) in or on:

Apples	0.5 ppm
Grapes	1.0 ppm

b. Tolerances for combined residues of RH-3866 and its RH-9090 (free and bound) and diol metabolites in:

Milk	0.05 ppm

c. Tolerance for combined residues of RH-3866 and its RH-9090 (free) metabolite in:

Meat, fat, and meat by-products (except liver) of cattle, goats, hogs, horses, and sheep	0.05 ppm
Liver of cattle, goats, hogs, horses, and sheep	0.3 ppm
Meat, fat, and meat by-products of poultry	0.02 ppm
Eggs	0.02 ppm

For ~~21 CFR 193.XXX:~~ 40 CFR 185.4350:

Tolerances for combined residues of RH-3866 and its metabolite RH-9090 (free and bound) in:

Raisins	10.0 ppm

For ~~21 CFR 561.XXX:~~ 40 CFR 186.4350:

Tolerances for combined residues of RH-3866 and its metabolite RH-9090 (free and bound) in:

Apple pomace (wet and dry)	5.0 ppm
Grape pomace (wet and dry)	10.0 ppm
Raisin waste	25.0 ppm

(#0246j/117j)
8/12/88

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FORM 208

ATTACHMENT 2

INTERNATIONAL RESIDUE LIMIT STATUS

T. Love 11/7/88

CHEMICAL Myclobutanil

CODEX NO. _____

CODEX STATUS:

☑ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Crop(s)	Limit (mg/kg)

PROPOSED U.S. TOLERANCES:

Petition No. 7F3476

RCB Reviewer Nelson

Residue: per Attachment 1

Crop(s)	Limit (mg/kg)

see Attachment 1.

CANADIAN LIMITS:

☑ No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES:

Form revised 1986

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