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

DEC 29 1986

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: IC-310. Farnesol and Nerolidol (Stirrup M): Request For Exemption from the Requirement of Tolerance Under 40CFR§180.1001 (d). Accession No. 264423. RCB No.1390.

FROM: Sami Malak, Ph.D., Chemist
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

THRU: P. V. Errico, Head
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

TO: Bhushan Mandava, PM#45
Registration Support and Emergency Response Branch
Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Technology Service Group on behalf of Fermone Chemicals, Incorporated of Phoenix, Arizona requests the following:

1. A registration for Stirrup-M as a pesticide product to be used in conjunction with other registered miticides,

2. A general exemption from tolerance for the active ingredients in Stirrup-M.

3. A clearance for use of Stirrup-M as an inert ingredient in registered miticides.

4. A special exemption from tolerance for use of Stirrup-M as an inert additive in registered miticides.

In the cover letter dated August 20, 1986, and elsewhere in this submission, the petitioner stated that synthetic farnesol and nerolidol are two active ingredients in Stirrup M possessing pheromonal activities intended for use in combination with miticides in the supression of Tetranychid mite species. An exemption from the requirement of tolerance for the inert ingredient nerolidol [3,7,11-Trimethyl-1,6,10-dodecatriene-3-ol] was previously requested in connection with PP#6E3795. RCB recommended for the exemption from the requirements of tolerance, pending TOX's assessment as to the need for actual field residue data and submission by the applicant complete information regarding the proposed use (PP6E3395, memo of R. W Cook, 8/22/86).

TOX did not object to exempting nerolidol for use as an inert ingredient and stated that nerolidol is a naturally occurring flavoring substance widely used in foods and that the synthetic version is cleared as a direct food additive under 21CFR§172.515 (PP#6E3395, memo of D. R. Ritter, 9/5/86).

In a letter dated September 17, 1986 (memo of Fred Betz of SIS to Willie Nelson of RD), HED has concluded that Farnesol and Nerolidol are biochemicals, both substances are naturally occurring plant constituents-terpene alkaloids which are claimed as having pheromonal activity. Mr. Betz advised the applicant, Fermone Chemicals, Inc., to substantiate that the synthesized substances are identical or substantially similar to the naturally occurring products. Mr. Betz stated that the active ingredients (Farnesol and Nerolidol) should be reviewed as bichemical food use pesticides and that the inert ingredients must be checked to assure that they are cleared for food use products.

Farnesol, which is the second active ingredient in Stirrup M, [3,7,11-Trimethyl-2,6-10-dodectriene-1-ol] is a naturally occurring flavoring substance widely used in foods and that the synthetic version, as the case with nerolidol, is cleared as a direct food additive under 21CFR§172.515. After discussing these issues with Fred Betz of SIS and Dave Ritter of TOX, it is RCB's assessment that the second active ingredient in Stirrup M known as Farnesol, should be reviewed in this memo under an F petition for an exemption from the requirements of a tolernce, and not as an inert ingredient. The submitted manufacturing processes for both active ingredients, formulations, the product chemistry data, uses, analytical methods, and other pertinent data made available to RCB are reviewed in this memo under the number assigned by the Product Manager (PM) for inerts, IC-310. The PM is notified (see following Recommendations) to re-classify this action under an F petition.

Conclusions

1(a). There are numerous literature citations regarding farnesol and nerolidol. The occurrence of these products is reported in several natural sources including oils of citronella, essential oils of neroli, ylang-ylang, lemon grass, tuberose, rose, musk, Peru balsam, sweet orange, in currant aroma, and numerous other natural sources.

1(b). The petitioner is requested to provide the following information showing that synthesized farnesol and neroldiol are identical or substantially similar to the naturally occurring products: (a) mass spectra for the naturally occurring substances; and (b) the conditions and parameters of the mass spectra used to identity the natural and synthetic products (spectra for the synthetic products are included in Accession #264423, submitted on 8/20/86).

1(c). Both farnesol and nerolidol are cleared as synthetic flavoring substances and adjuvants under 21CFR§172.515.

2(a). The unintentional impurities formed during the manufacturing process of farnesol and nerolidol are closely related compounds to the active ingredients with very low concentrations and are not expected to present a residue problem.

2(b). We defer to the Registration Division for their assessment on the clearance of the inert ingredients in Stirrup M for food uses (EPA Reg. No. 53871-E).

3(a). A capillary column GC-mass spectrometry method was employed for the anlaysis of the two active ingredients in Stirrup M, farnesol and nerolidol, as well as major impurities present in the manufacturing use products (MUP's).

3(b). For the purpose of the proposed use, there is no need to develop an analytical method for residue determination of farnesol and nerolidol in or on treated plant commodities.

4. The petitioner is advised to revise section B showing the chemical names of the active ingredients, farenesol and nerolidol on the front pannel of the proposed label.

5. After compliance with Conclusions 1(b) and 4; and after RD's assessment on the inert ingredients as requested in Conclusion 2(b), RCB can conclude that there will be no residue problem for farnesol or nerolidol, the two active ingredients in Stirrup M, in/on the treated plant commodities.

6. Based on the proposed low application rates and provided that the petitioner complies with data gap cited under Conclusion 1(b) and 4; and after RD's assessment of the inert ingredients as requested in Conclusion 2(b), RCB can conclude that there will be no problems of secondary residues in meat, milk, poultry, and eggs.

7. Since this action is reviewed as an exemption from the requirements of a tolerance, we are not concerned with International Tolerances at this time.

Recommendations

TOX considerations permitting and provided that the petitioner complies with Conclusions 1(b) and 4; and after RD's assessment on the inert ingredients in Stirrup M as requested under Conclusion 2(b), RCB can recommend for exemption from the requirements of a tolerance for residues of farnesol and nerolidol in or on treated plant commodities.

Note to the PM

This action should be re-classified properly under an F petition for an exemption from the requirements of a tolerance rather than inerts under the assigned number IC-310.

DETAILED CONSIDERATIONS

Manufacturing Process

The manufacturing process for farnesol and nerolidol, the two active ingredients in Stirrup M, are adequately described. A summary of the manufacturing process is presented in Confidential Appendix I (three pages).

The upper and lower limits of each active ingredient and unintentional impurities formed during the manufacturing process of farnesol and nerolidol are discussed below under Certification of Limits. Each of these two process result in what is referred to as Manufacturing Use Product (MUP).

[redacted]

It is RCB's assessment that unintentional impurities formed during the manufacturing and purification process of farnesol and nerolidol are closely related compounds to the active ingredients with very low concentrations and are not expected to present a residue problem.

The petitioner is requested to provide the following information showing that synthesized farnesol and nerolidol are identical or substantially similar to the naturally occurring substances: (a) mass spectra for the naturally occuring substances; and (b) the conditions and parameters of the mass spectra used to identify the natural and synthetic products (spectra for the synthetic products are included in Accession # 264423, submitted on 8/20/86).

Analytical Method for Batch Analyses

Both farnesol and nerolidol were analyzed for their major components and impurities using capillary column GC-mass spectrometry. The upper and lower limits of each component are discussed below under Certification of Limits. The GC and mass spectra for each component are included in this submission. The GC parameters were adequately described.

Certification of Limits

The analysis included in this submission is for five randomly selected production batches (MUP's) of farnesol and nerolidol. The upper and lower limits for the active and unintentional impurities in both products are presented in Confidential Appendix II (one page). The nominal concentrations of the active components of the MUP's, farnesol and nerolidol were reported at 99.2 and 98.7% by weight, respectively. That for the inerts in farnesol and nerolidol were reported at [redacted] and [redacted] respectively.

Formulation

See Confidential Appendix III (one page). The formulation of the End Use product (EUP), Stirrup M contains the two active ingredients, farnesol and nerolidol. On the product label (EPA reg. No. 53871-E), the active ingredients are referred to as Multi-methyl alkenols accounting for 1.76% by weight and the inerts are referred to as Release Agents accounting for 98.4% by weight.

Multi-methyl alkenols for the name of the active ingredients is not specific enough. The front pannel of the proposed label must bear the chemical name of the active ingredients. The petitioner is advised to revise section B showing the chemical names of the active ingredients, farenesol and nerolidol on the front pannel of the proposed label.

Impurities accounting for a maximum concentration of 0.03% by weight in the EUP and are not expected to present a residue problem.

We defer to the Registration Division for their assessment on the clearance of the inert ingredients in Stirrup M for food uses (EPA Reg. No. 53871-E).

Physical and Chemical Properties

The physical and chemical characteristics for the two active ingredients in Stirrup M, farnesol and nerolidol, were reported by the petitioner as Confidential. These are presented in Confidential Appendix IV (one page).

Proposed Use

Stirrup M, a behavior modifying biochemical possessing pheromonal activity is recommended for use in combination with registered miticides for control of Tetranychid mite species infesting various field crops; tree fruits; nuts; and greenhouse and outdoor ornamentals. The product may

be applied as needed using ground or aerial equipment at the rate of 0.035 to 0.1 oz act/A/application in water or vegetable oil. The frequency of applications and intervals between applications recommended on the registered miticide labels are to be observed.

Analytical Methodology for Residue Determination

No analytical methodology for residue determination of farnesol and nerolidol in/on treated plant commodities was submitted. For the purpose of the proposed use, there is no need to develop a method.

Nature of Residues

In this submission, no description of the residue is submitted.

There are numerous literature citations regarding farnesol and nerolidol. The occurrence of these products is reported in several natural sources including oils of citronella, essential oils of neroli, ylang-ylang, lemon grass, tuberose, rose, musk, Peru balsam, sweet orange, in currant aroma, and numerous other natural sources [Fenaroli's Handbook of Flavor Ingredient, Condensed Chemical Dictionary 8th ed., Merk Index 9th ed, and Food Chemicals Codex].

Residue Data

No residue data are submitted.

The active ingredients in Stirrup M, farnesol and neroldiol, are two naturally occurring flavoring substances widely used in foods and that the synthetic versions are cleared as direct food additives under 21CFR§172.515. This should be further augmented by the petitioner by showing that synthesized farnesol and nerolidol are identical or substantially similar to the naturally occurring products. After receiving these data (verifying that synthetic farnesol and nerolidol are identical or substantially similiar to the naturally occuring products), and after revising Section B as requested under Formulation; and clearance of the inert ingredients by the Registration Division for food uses, RCB can conclude that there will be no residue problem for farnesol and nerolidol in or on the treated plant commodities and recommend for an exemption from the requirements of a tolerance.

Meat, Milk, Poultry, and Eggs

No animal feeding or metabolism studies are submitted. Based on the proposed low application rates and provided that the petitioner complies with data gaps concerning the similarity between the synthetic and naturally occurring farnesol and nerolidol, as well as revising Section B and clearance of the inerts by the Registration Division for food uses, RCB can conclude that there will be no problems of secondary residues in meat, milk, poultry, and eggs.

International Tolerances

Since this action is reviewed as an exemption from the requirements of a tolerance, we are not concerned with International Tolerances at this time.

Attachments: Confidential Appendices I to IV.

I. Manufacturing process of farnesol and nerolidol(3 pages).
II. Certification of Limits(one page).
III. Formulation(one page).
IV. Physical and Chemical Properties(one page).

cc With Attachments: RF, TOX, SF (Stirrup M or farnesol/nerolidol), Inert Ingredients File (M. Bradley), PP#6E3395, S. Malak, RD [PM #'s 45 (Mandava) and 17 (Willie Nelson)], and PMSD/ISB.

cc Without Attachments: Circu, EAB, EEB, FDA, and Robert Thompson (RTP).

RDI: P. V. Errico: 12/19/86: R. D. Schmitt: 12/29/86.
TS-769:RCB:CM#2:RM:814A:S.Malak:X557-4379:11/21/86