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

Memorandum: MAR 22 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#1G3930. Temporary Tolerance and Experimental Use Permit for Use of Avermectin B_1 on Apples. EUP-618. (No MRID #. DEB#7427).

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and

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Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., proposes a temporary tolerance be established for the residues of the miticide avermectin B_1 and the delta 8,9 geometric isomer of avermectin B_{1a} in/on apples (fresh market only) at 0.035 ppm. (A synonym for avermectin B_1 is abamectin). Avermectin B_1 is defined as a mixture of avermectins containing $\geq$ 80% avermectin B_{1a} (5-0-demethyl avermectin A_{1a}) and $\leq$ 20% avermectin B_{1b}(5-0-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)avermectin A_{1a}). Tolerances, all with expiration dates of 3/31/93, are established for residues of avermectin B_1 and its delta 8,9 isomer in/on cottonseed (0.005 ppm), citrus whole fruit (0.02 ppm), cattle meat (0.02 ppm), cattle meat byproducts (0.02 ppm), and milk (0.005 ppm). Food additive tolerances are established, all with an expiration date of 3/31/93, for citrus oil (0.10 ppm) and citrus pulp, dried (0.1 ppm).

Tolerances are pending for residues of avermectin B_1 and its delta 8,9-isomer in/on r.a.c.'s of tomatoes (0.005 ppm), celery (0.035), pears (0.035 ppm), and strawberries (0.025 ppm). Food additive tolerances are pending for tomato pomace (0.07 ppm dry, 0.01 ppm wet).

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For this EUP, the proposed use is the following:

A single rate of 0.025 lb a.i./A + 1.0 gallon oil/A will be applied twice in a 4 tree X 4 tree design with the four center trees used for sampling. The spray will be delivered in a minimum of 40 gpa for concentrated tests and up to 500 pga for dilute tests. A total of 150 acres are requested for the tests which are spread over 13 states (state, acres: WA, 35; NY, 20; MI, 15; PA, 15; CA, 14; VA, 8; NC, 8; WV, 5; OR, 5; ID, 5; OH, 5; CO, 5; ME, 5; NJ, 5). The total a.i. (avermectin B_1) for the trials is 7.5 lb. Treated apples will only be harvested for fresh market sales; apples treated in this experimental program will not be processed into food/feed products. The proposed experiment will be run between April 1, 1991 and December 31, 1991. The objectives of the experimental use permit are to determine efficacy, phytotoxicity, and product performance under different application rates.

Summary of Comments/Conclusions:

1. The manufacturing process has been adequately discussed and impurities are not likely to be a residue problem.

2. The directions for use are adequate.

3. For the purposes of this temporary tolerance only,

   a. The nature of the residue, avermectin B_1 and its delta 8,9 isomer, is adequately understood.

   b. Additional animal metabolic data are not needed.

   c. The analytical methodology is adequate for the determination of avermectin B_1 and its delta 8,9 isomer in apples.

   d. The pear storage stability data can be used to support the experimental use of avermectin B_1 on apples.

   e. Residue data will be translated from pears to apples to support the proposed 0.035 ppm tolerance for apples in this EUP only.

   f. No residue data for processing studies are required.

   g. Secondary residues are not expected in meat, milk, poultry, or eggs.

4. For the purposes of a permanent tolerance, the petitioner must supply

   a. Residue data for apples and processed products.

   b. Storage stability data for r.a.c apples and processd products.

   c. Analytical methodology with validation data.

   d. Possibly additional plant and animal metabolic studies.

5. There are no compatability problem with Codex, or Canadian, or Mexican limits.

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Comments/Conclusions:

1. The manufacturing process has been adequately discussed in previous tolerance requests. CBTS concludes that impurities are not likely to be a residue problem.

2. The directions for use are adequate.

3. Plant metabolism data were not submitted with this petition. Data were previously submitted for celery, cottonseed, and citrus. CBTS has expressed the possible need for additional plant studies to support other commodities, particularly if the use pattern differs significantly from those on cotton, citrus, celery, or tomatoes. However, the nature of the residue is understood for the purposes of this temporary tolerance. The residues of concern are avermectin B_1 and its delta 8,9 isomer.

4. Animal metabolism data were not submitted with this petition. Although wet and dry apple pomace are animal feed items, these studies will not be needed for this temporary tolerance because the treated apples will not be processed into food/feed items. In addition, only 150 acres over a 13 state area are proposed in this experimental program.

5a. The proposed analytical methodology (Method No. 8000) is the same as submitted for pears. This methodology is current under study at the EPA laboratory at Beltsville. An independent method validation on the pear method had been submitted in PP#9F3787 in the request for a pear tolerance.

5b. A successful petition method validation (PMV) has been completed for methodology for citrus and submitted to FDA for inclusion in PAM II as Method I. A letter method has also been submitted to FDA for cottonseed.

5c. For the purposes of this temporary tolerance only, analytical methodology is adequate for the determination of avermectin B_1 and its delta 8,9 isomer in apples.

5d. There is an enforcement method for the determination of avermectin B_1 and its delta 8,9 isomer in animal commodities.

6. No storage stability data are submitted in this petition. The petitioner has requested the data submitted for pears be translated for apples. For the purposes of this temporary tolerance only, the pear data can be used to support the experimental use of avermectin B_1 on apples.

7. No residue data were submitted for apples. The petitioner has requested that the pear residue data be translated from pears to apples. For the purposes of this EUP only, these data can adequately be translated. The data support the proposed 0.035 ppm tolerance for apples at the proposed 30 day PHI.

8. Secondary residues are not expected in meat or milk because the apples treated in this EUP will not be processed. Likewise, no residues are expected in poultry or eggs.

9. There are no Codex, Canadian, or Mexican limits established for avermectin B_1 or the delta 8,9 geometric isomer of avermectin B_1. Therefore, no compatability problem exists.

Recommendations:

CBTS can recommend for the establishment of the requested temporary tolerance for the combined residues of avermectin B_1 and its delta 8,9 isomer in/on apples at 0.035 ppm.

For a permanent tolerance for apples the petitioner is advised to follow 40 CFR 158 and the Residue Chemistry and Product Chemistry Guidelines. We further advise the petitioner to address the following requirements for a permanent tolerance.

* Residue data must reflect the proposed use on apples at the maximum rate and the minimum proposed 30 day PHI. An adequate geographical representation of major apple growing areas should be submitted.

* Residue data for processed apple commodities (juice, wet and dry pomace) from crop treated at the maximum application rate and the minimum PHI.

* Storage stability data of avermectin B_1 and its delta 8,9 isomer in r.a.c. apples, and in apple juice and pomace (wet and dry).

* Provide validation and recovery data using the proposed analytical methodology.

* The petitioner should be prepared to conduct additional plant metabolism studies if the use patterns differ significantly from those registered/proposed for apples, pears, cotton, celery, citrus, or tomatoes.

* The petitioner should provide a new goat metabolism study, with ^{14}C-labelled material, at elevated feeding levels if the dietary burden to livestock is increased by the proposed use on apples.

Detailed Considerations

Manufacture and Formulation

Avermectin B_1 is produced by a fermentation process using a strain of Streptomyces avermilitis. This process yield 4 nomologous pairs of closely related compounds: avermectin A_1, A_2, B_1, and B_2. The avermectins are extracted from the culture broth and purified by recrystallization. Avermectin B_1

is the technical grade active ingredient in the proposed formulation. The manufacturing process for technical avermectin B_1 and its contents have been discussed previously (PP#4F3065, memo of 9/13/84, V. Frank Boyd; PP#5G3287, memo of 12/10/85, L. Cheng). The TGAI contains ca 1% of unidentified impurities related to the avermectins. The TOX Branch has stated that the impurities are not of concern (PP#5G3287, memo of 3/12/86, W. Dykstra). CBTS concludes that the impurities are not likely to be a residue problem, and there are no problems with the manufacturing process.

The formulated product is AGRI-MEK 0.15 EC Miticide/Insecticide. One gallon of the emulsifiable concentrate (EC) contains 0.15 lbs avermectin B_1 as the active ingredient. Clearance of the inert ingredients under §180.1001 is within the purview of the Registration Division.

The label describes the a.i. as avermectin B_1:[a mixture of avermectins containing $\geq$ 80% avermectin B_{1a} (5-0-demethyl avermectin A_{1a}) and $\leq$ 20% avermectin B_{1b}(5-0-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a})]. Avermectin B_1 is 2.0% of the formulated product.

Proposed Use

For control of mites and other damaging insects on apples during mid-to-late season, the above formulation is applied at 10-20 fl. oz./A (0.0125 - 0.025 lb. a.i./A), not to exceed more than 20 fl. oz./A per application or 40 fl. oz./A/season, in a minimum of 40 gallons of water per acre for concentrated sprays and up to 500 gallons of water per acre for dilute sprays. Applications are made with a paraffinic oil in both the dilute and concentrated sprays with no more than 1.0 gallon of paraffinic spray oil per acre in the finished spray. Only ground equipment should be used. The proposed PHI is 30 days and grazing of the treated orchards is not permitted.

Nature of the Residue:

Plants: No new plant metabolism data were submitted in this petition. Data were previously submitted on celery, cottonseed, and citrus (PP#'s 5G3220, 5G3287, and 8F3649). The petitioner has also submitted a report entitled "Comparative Degradation of Avermectin B_{1a} in Cotton Leaf, Citrus Fruit, Celery and In Vitro" (MRID#408709-19). The degradation of 14C or 3H-avermectin B_{1a} on citrus fruit, cotton leaves, and celery from plant exposed to sunlight was compared to 14C-avermectin B_{1a} degradation on glass under simulated sunlight by HPLC analysis of the residues. Details of the studies were discussed previously (See memos of: 12/15/89, S. Willett, PP#9F3703; 7/89/87, C. Deyrup; 11/16/88, V. F. Boyd; 2/13/89, V. F. Boyd).

In general, the cochromatography of the solvent rinses of the 14C-treated plant with standards, according to the petitioner showed the following:

1. The degradation of avermectin B_1a on plants or in vitro appears to be similar and results in a complex mixture.

2. At least 2 avermectin B_1a degradates were formed in all systems examined; the conformational isomer of the parent compound, delta 8,9 avermectin B_1a, and an oxygenated product of the parent compound, 8-alpha hydroxy avermectin B_1a.

3. When the proportion of avermectin B_1a is less than 10-15% of the total remaining residue, which usually occurred in a week or less post-application in plants, most of the remaining residue is present as unidentified multiple polar compounds which appear to degrade slowly with extended exposure to sunlight.

4. The studies indicate that photodegradation on plant surfaces rather that metabolism is the major pathway for avermectin B_1a disposition in plants.

CBTS previously agreed that the metabolism of avermectin B_1 in plants is complex with the parent compound and its delta 8,9 isomer accounting for 10% or more of the total residue. A small amount has been identified as an alpha-8-hydroxy degradate, and the remaining terminal residue is composed of several unidentified polar degradates. The petitioner has submitted data to show that the residues present in the citrus surface rinses, celery extracts, and cotton leaf rinses and extracts at typical PHI's are similar to in vitro photodegradation products. To support the uses on cotton and citrus, the polar degradates generated on citrus (30X, 7 day PHI) and in vitro (30 hr sample) have been tested for toxicity and were found to be of no toxicological significance at the levels tested (See TOX memos 007080 and 007801 of W. Dykstra dated 3/13/89, and DEB memo of V. F. Boyd dated 6/21/89).

DEB also commented previously that we do not agree with the petitioner's conclusion that avermectin B_1 is degraded on all plants in a similar manner. The metabolism is complex and may need additional studies. Photodegradation on the exterior plant surfaces is not the only transformation taking place on plants, and may not necessarily always be the major degradative pathway under certain conditions. The petitioner should be prepared to conduct additional plant metabolic studies on other crops to support future uses, particularly if the use pattern differ significantly from those of cotton, celery, citrus and tomatoes. In future studies, C14-treatment should more closely simulate actual use (e.g. incidential application to soil, etc.). The accountability of the total radioactivity should be improved. A 14C-labelled compound should be used.

For the purpose of establishment of a temporary avermectin B_1 tolerance in/on apples, the metabolism data is adequate. The residue of regulatory concern is avermectin B_1 and the delta 8,9 geometric isomer of avermectin B_1a.

Animals: No additional animal metabolism data were submitted in this petition. Although apple pomace (wet and dry) is considered animal feed items, the petitioner has stated that the apples will only be marketed as fresh, and will not be processed into food/feed products. In addition, the proposed treatment of 150 acres spread over a 13 state area would be small and would not require additional animal metabolism data to support this EUP or a temporary tolerance.

For a permanent tolerance in/on apples, the petitioner is advised of CBTS's previous comments (See memo of 12/15/89, S. Willett, PP#9F3703) that if registration on additional fed items causes the dietary burden in livestock to increase, a new C14 goat metabolism study may be required.

Analytical Methodology

Analytical methodologies have been previously submitted for citrus, tomato, celery, cottonseed, and pears. The methodology used for pears is proposed for apples. In all methods residues of avermectin B_1 and its delta 8,9 isomer are extracted into organic solvents, passed through cleanup procedures, derivatized, and quantified by reverse phase HLPC with fluorimetric detection. The methods are summarized in the following table.

As evidenced in this table the initial plant extractions and cleanup procedures differ amongst the commodities. A successful validation by the Agency has been completed for Method No. 1009R3 (citrus) and has been submitted to FDA for inclusion in PAM II as Method I. Method No. 6004 (cottonseed) has been submitted to FDA for inclusion in PAM II as a letter method since a method trial was not run by the Agency, but the methodology maybe adequate for enforcement purposes.

The method of choice for avermectin B_1 residues on apples is No. 8000, the one submitted for pears (PP#9F3787). This method differs initially from the others in that an enzymatic step is necessary before the plant matrix can be adequately extracted for avermectin B_1 residues (See memo of 7/10/91, L. Grosso, Merck Regulatory Affairs, PP#9F3787). Except for the enzymatic step, Method No. 10001R1 (celery) appears to be identical to No. 8000, but this celery method has not been run in the agency laboratory. Method No.8000 has been submitted to the EPA laboratory in Beltsville for method validation in pears. All the methods, after differences in the extraction procedures and sample cleanups, use the same derivatization step and reverse phase HPLC analysis of the fluorescent derivatives.

The petitioner has submitted method validation data from an independent laboratory in the petition for pears (#9F3787, MRID# 411885-12). Two fortification levels for avermectin B_1a and the delta 8,9 isomer (5.0 and 25.0 ppb, and 4.5 and 22.7 ppb, respectively) and one level for the avermectin B_1b (5.6 ppb) were used. Recoveries ranged from 90 to 103 % for avermectin, and 74 to 98% for the delta 8,9 isomer using Method No. 8000. Additional validation data for pears, has also been submitted in

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Summary of Avermectin B_1 analytical methods submitted to CBTS:

Citrus, Method No. 1009R3[a]	Tomato, Method No. 9003	Celery, Method No. 10001R1	Pears, Method No. 8000	Cottonseed, Method No. 6004[b]
MeOH extraction	MeOH extraction	CH_3CN/H_2O extraction	Enzymatic hydrolysis; CH_3CN/H_2O extraction	MeOH extraction; Cleanup on aminopropyl column
Solvent partition isooctane/CH_2Cl_2	Solvent partition isooctane/CH_2Cl_2	Cleanup on C8 column, CH_3CN eluant	Cleanup on C8 column, CH_3CN eluant	Solvent partition, isooctane/CH_2Cl_2; Cleanup on C8 column
Cleanup on acidic alumina column, CH_2Cl_2 (1% isoPrOH)	Cleanup on acidic alumina column, CH_2Cl_2 (1% isoPrOH)	Hexane extraction; aminopropyl column, hexane/toluene/ CH_2Cl_2/acetone	Hexane extraction; aminopropyl column, hexane/toluene/ CH_2Cl_2/acetone	Solvent partition, hexane/CH_3CN
TFAA/1-MI/DMF; MeOH/NH_4OH; Silica cleanup, $CHCl_3$	TFAA/1-MI/DMF; MeOH/NH_4OH; Silica cleanup, $CHCl_3$	TFAA/1-MI/DMF; MeOH/NH_4OH; Silica cleanup, $CHCl_3$	TFAA/1-MI/DMF; MeOH/NH_4OH; Silica cleanup, $CHCl_3$	TFAA/1-MI/DMF; MeOH/NH_4OH; Silica cleanup, $CHCl_3$
HPLC C18 column, MeOH/H_2O (9:1)	HPLC C18 column MeOH/H_2O (9:1)	HPLC C18 column MeOH/H_2O (9:1)	HPLC C18 column MeOH:H_2O (9:1)	HPLC C18 column MeOH/H_2O (9:1)

a A successful PMV has been completed and the method has been sent to FDA for inclusion in PAM II as Method I.

b The method has been submitted to FDA for inclusion in PAM II as Method IA.

the aforementioned petition (MRID#s 411885-11 and 4111885-15). The pear matrix fortifications ranged from 5.0 to 50.0 ppb for avermectin B_1a, 3.7 to 3.8 ppb for avermectin B_1b, and 4.6 to 46 ppb for the delta 8,9 isomer. Recoveries ranged from 55 to 100% (B_1a, 24 samples, 85% ave.), 53 to 103% (B_1b, 8 samples, 86% ave.), and 57 to 99% (delta 8,9 isomer, 26 samples, 84% ave.). Control samples were adequate. The limit of detection is 0.02 ppm.

Therefore, for the purposes of this EUP only, the analytical methodology will be adequate to support the temporary 0.035 ppm tolerance in/on apples. However for a permanent tolerance on apples, this method (No. 8000) must successfully pass the Agency laboratory validation. If another method is proposed for enforcement, then CBTS must review this new method and supporting validation data.

Storage stability data have not been submitted for apples, but the petitioner has requested the translation of the pear data (PP#9F3787, MRID# 411885-14) to support this EUP for apples. Four set of samples were fortified with avermectin B_1a (10.2 or 71.0 ppb), B_1b (10.0 ppb), or delta 8,9 isomer (5.3 ppb). Samples were stored frozen and analyzed at 43, 92, 183, and 365 days. Two replicates were run for each fortification (except 3 for 10.2 ppb B_1a) with recoveries ranging from 62 to 111%, with averages of 86% for B_1a, 89% for B_1b, and 93% for delta 8,9 isomer. One sample of B_1a gave 0% recovery, but it was questioned if the sample received the initial fortification. A freshly fortified sample (10.2 ppb B_1a) run in parallel gave 85% recovery. Control data were adequate.

Therefore for the purposes of this EUP only, the pear storage stability data will be translated to support the proposed experimental use of avermectin on apples. However for a permanent tolerance on apples, adequate storage stability data for the r.a.c. and any processed products for avermectin B_1 treated apples must be submitted to the Agency.

Residue data

No residue data are submitted for apples. The petitioner has requested that the data submitted for pears (PP#9F3787) be translated to support the experimental use on apples.

Avermectin B_1 residue data has been submitted for pears from CA, CO, NJ, NY, OR, PA, and WA. The data reflect 1X (0.025 lb a.i./A) and 2X (0.05 lb a.i./A) rates at a 14-day PHI. The spray volumes were applied from 34 to 53 gpa and from 250 to 400 gpa. The number of applications per season was 3 in 7 field trials and 4 in 25 field trials. At the proposed 14-day PHI, the combined residues of avermectin B_1 and its delta 8,9 isomer, ranged from nondectable (ND:<0.02 ppm) to 24.2 ppm at the proposed 1X rate, and from ND to 81.2 ppm at the 2X rate. The 2X rate (0.05 lb a.i./A) is the maximum allowed per season.

The proposed application rate for apples, i.e., 40 to 500 gpa at 0.025 lb a.i./A, twice a season, is similar to that proposed for pears. In addition the pears have a 14-day PHI; the proposed PHI for apples is a 30-day PHI.

Based upon the residue data for pears, and the proposed application scheme, the proposed 0.035 ppm tolerance would adequately cover any avermectin B_1 residues in/on treated apples. Therefore, for the purposes of this EUP only, the pear residue data can adequately be translated in support of the purposed experimental use of avermectin B_1 on apples and a temporary tolerance of 0.035 ppm on apples.

The petitioner should be advised that a permanent tolerance on apples will require adequate residue data for avermectin B_1 treated apples at the maximum rate and the minimum PHI which are representative of the major US apple growing states.

No processing studies are submitted in this petition. However, since the petitioner has designated that the treated apples harvested from the 150 acres spread over a 13 state area will not be processed, but will be marketed only as fresh apples, then for the purposes of this EUP only, processing studies will not be required. However, for a permanent tolerance for apples, the petitioner must also supply an adequate processing study to support any food/feed additive tolerances that might be needed.

Meat, milk, poultry, and eggs

Temporary tolerances are established for avermectin B_1 and its delta 8,9 isomer in cattle meat and meat byproducts (0.02 ppm) and milk (0.005 ppm) with an expiration date of 3/31/93.

Apple pomace (wet and dry) is an animal feed item. Dry pomace may comprise upto 50% of the beef cattle diet, upto 25% of dairy cattle diet, and upto 5% of turkey and broiler diets. Laying hens and swine are not normal fed apple pomace. In this petition, however, the treated apples will not be processed. Thus, apple pomace will not be available for animal feeding. Therefore, there is no reasonable expectation of finite residues in livestock with this experimental use of avermectin B_1 on apples.

No changes in the tolerances are necessary at this time. However, if a permanent tolerance is established on apples, then the dietary burden of livestock must be reviewed to determine the need for any tolerance increases, if necessary, in meat, meat byproducts, poultry, and milk.

Other considerations

There are no Codex, Canadian, or Mexican limits established for avermectin B_1 or the delta 8,9 geometric isomer of avermectin B_1. Therefore, no compatability problem exists.

cc: PP#9F3787; J. Stokes (CBTS); C. Furlow (PIB/FOD); Avermectin B_1 S.F.; R. Schmitt; R.F.; Circulation (7)
RDI: PErrico:3/14/91:RLoranger:3/14/91
H7509C:CBTS:JStokes:js:Rm 803C:CM#2:557-1478:3/18/91