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

Memorandum: JUL 9 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#9F3787. Avermectin B_1 in/on pears. Evaluation of Analytical Method and Residue Data. (MRID#'s 412064-01, 411885-01, -02, -03, -04, -05, -06, -07, -08, -09, -10, -11, -12, -13, -14, -15, and -16, DEB#5700).

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THRU: Richard D. Schmitt, Ph.D., Chief
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TO: George LaRocca, PM-15
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and

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Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., proposes a 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 pears 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 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 (0.05), and strawberries (0.02 ppm). A temporary 0.035 ppm tolerance for

apples was recently recommended by CBTS (See memo of 3/22/91, J. Stokes). However, CBTS has now decided to recommend an increase of the 0.035 ppm temporary tolerance to 0.05 ppm since the 0.035 ppm recommendation is based upon the pear residue data. Food additive tolerances are pending for tomato pomace (0.07 ppm dry, 0.01 ppm wet).

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

4. Additional animal metabolic data are not needed.

5. The analytical methodology for pears must pass a successful petition method validation.

6. The pear storage stability data can be used to support the proposed use of avermectin B_1 on pears.

7. The proposed 0.035 ppm tolerance for pears is not adequate. A revised Section F should be submitted to request a tolerance of 0.05 ppm in pears.

8. No residue data for processing studies are required.

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

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

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 tolerance in/on pears. The residues of concern are avermectin B_1 and its delta 8,9 isomer.

4. Animal metabolism data were not submitted with this petition. No animal feed items are associated with pears.

5a. The proposed analytical methodology (Method No. 8000) is currently under study at the EPA laboratory at Beltsville. An independent method validation on the pear method has been submitted in this pettion (PP#9F3787) for a pear tolerance. This method must pass a successful PMV before CBTS can recommend for a 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. Avermectin has been tested using the FDA multiresidue method protocol A, and the data previously sent to FDA 6/21/89.

6. Storage stability data are submitted in this petition. For the purposes of this tolerance, the pear data is adequate to support the proposed use of avermectin B_1 on pears.

7. Residue data were submitted for pears. The data do not support the proposed 0.035 ppm tolerance for pears at the proposed 14 day PHI. Extrapolation of residue data at the 2X rate shows that a 0.045 ppm tolerance would be adequate. The petitioner should submit a revised Section F requesting a tolerance of 0.05 ppm on pears.

8. Secondary residue are not expected in meat, milk, poultry, or eggs because pears are not used as animal feeds.

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 recommends against the establishment of 0.035 ppm tolerance for the combined residues of avermectin B_1 and its delta 8,9 isomer in/on pears because of conclusions 5a and 7. The analytical methodology must pass a successful petition method validation and a revised Section F is needed.

Detailed Considerations

Manufacture and Formulation

Avermectin B_1 is produced by a fermentation process using a strain of Streptomyces avermilitis. This process yield 4 homologous 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 formulation to be discussed. 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. The inert ingredients are cleared for use under §180.1001.

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 pear psylla during mid-to-late season, apply 10-20 fl. oz./A (0.0125 - 0.025 lb. a.i./A). Do not exceed 40 fl. oz./A/season. Apply in minimum 40 gallons of water per acre for concentrated sprays and up to 400 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 14 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 memoes 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 memoes 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. accidential application to soil, and moderate rainfall). The account of the total radioactivity should be improved. A 14C-labelled compound should be used. (See memo of 12/15/89, S. Willet, PP#9F3703).

For the purpose of establishment of an avermectin B_1 tolerance in/on pears, the metabolism data is adeqaute. 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. CBTS had previously commented that if registration on additional feed items causes the dietary burden in livestock to increase, a new C14 goat metabolism may be required. (See memo of 12/15/89, S. Willett, PP#9F3703). However, the pear is not considered an animal feed item. Therefore, for the purposes of the

establishment of a avermectin B_1 tolerance in/on pears, additional animal metabolic data will not be needed.

Analytical Methodology

Analytical methodologies have been previously submitted for citrus, tomato, celery, cottonseed, and pears. Methodology is submitted in this petition. 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 fluormetric 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. Method No. 1009R3 (citrus) has completed a successful validation by the Agency, and has been submitted to FDA from 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 is adequate for enforcement purposes.

The method of choice for avermectin B_1 residues on pears is No. 8000. 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, also been submitted in 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 0.002 ppm.

To assure the adequacy as an enforcement method, the analytical methodology (Method No. 8000) must successfully pass the Agency laboratory validation.

Commodity	Method No.	Matrix Extraction	Solvent Partition	Column Cleanup	Solvent Partition	Column Cleanup	Solvent Partition	Derivatization: HPLC Analysis
Citrus	1009R3[a]	Methanol	Isooctane/ methylene chloride	Acidic alumina: methylene chloride/ isopropanol	-----	-----	-----	↑
Cotton-seed	6004[b]	Methanol	-----	Aminopropyl: hexane/toluene/ methylene chloride/ acetone	Isooctane/ methylene chloride	C8: acetonitrile	Hexane/ acetonitrile	Trifluoro-acetic anhydride/ 1-methyl-imidazole/ dimethyl-formamide;
Tomato	9003	Methanol	Isooctane/ methylene chloride	Acidic alumina: methylene chloride/ isopropanol	-----	-----	-----	Methanol/ ammonium hydroxide;
Celery	10001R1	Acetonitrile/ water	-----	C8: acetonitrile	Hexane	Aminopropyl: hexane/toluene/ methylene chloride/ acetone	-----	Silica column: chloroform;
Pear	8000	Pectinase hydrolysis; Acetonitrile/ water	-----	C8: acetonitrile	Hexane	Aminopropyl: hexane/toluene/ methylene chloride/ acetone	-----	HPLC C18: methanol/ water

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.

Avermectin has been tested using the FDA multiresidue method protocol A, and the data previously sent to FDA. (See memo of 6/21/89, V. Boyd).

Storage stability data

Storage stability data are available for pears. (MRID#411885-14). Four sets of samples were fortified with avermectin B_{1a} (10.2 or71.0 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.

The storage stability data is adequate to support the propose use on pears.

Residue data

Residue data are submitted for pears.

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 0, 1, 3, 7 and 14-day PHI's. 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 ppb at the proposed 1X rate, and from ND to 89.7 ppb at the 2X rate. The 2X rate (0.05 lb a.i./A) is the maximum allowed per season. Details of the residue data are included in the following table.

Based upon the residue data for pears at the proposed application scheme, the proposed 0.035 ppm tolerance would not appear adequate to cover the avermectin B_1 residues in/on treated pears. The concentrated sprays (40 gpa) give consistly higher maximum residues than the more dilute spray solutions. At 14 days PHI, residues as high as 89.7 ppb at the 2X rate were reported. Extrapolating to the 1X rate, a tolerance of 0.05 ppm would be more appropriate for the proposed use. A revised Section F should be submitted.

No processing studies are submitted in this petition. Since tolerances are established only on the r.a.c., pears, then processing studies will not required.

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RESIDUE DATA 1987 FIELD TRIALS

Location/Study ID	lb a.i. /A[a]	Spray volume, GPA	No. of applications	Residue range, ppb (PHI in days) [b]		
				0	7	14
CA/001-87-5007R	0.025	300-400	4	9.4-22.5	NQ - 8.3	NQ - 9.2
CA/001-87-5007R	0.05	300-400	4	21.3-70.0	9.6-21.4	8.1-19.0
OR/001-87-5008R	0.025	40	4	17.4-32.3	8.6-18.9	11.4-24.2
OR/001-87-5008R	0.05	40	4	40.8-88.4	59.7-98.2	14.3-89.7
OR/001-87-5008R	0.025	250-400	4	10.8-15.6	NQ - 5.9	5.7-9.5
OR/001-87-5008R	0.05	250-400	4	29.9-45.3	26.1-32.4	12.0-19.5
CO/001-87-5009R	0.025	300	4	12.6-21.6	NQ - 10.0	ND - 5.8
CO/001-87-5009R	0.05	300	4	20.5-30.2	10.2-20.8	10.6-13.3
PA/001-87-5010R	0.025	250-400	4	17.0-25.6	8.9-13.1	7.0-10.4
PA/001-87-5010R	0.05	250-400	4	34.6-53.4	15.1-19.2	7.4-17.2
OR/001-87-5011R	0.025	360	4	6.9-15.4	ND - NQ	-----
WA/001-87-5012R	0.025	400	4	15.4-19.3	ND - NQ	-----
WA/001-87-5012R	0.025	40	4	8.2-18.6	ND - NQ	-----
NY/001-87-5013R	0.025	40	4	27.8-53.0	13.7-23.6	11.6-18.9
NY/001-87-5013R	0.05	40	4	57.6-88.4	25.0-34.2	15.0-25.8
NY/001-87-5013R	0.025	250-400	4	32.5-39.0	NQ - 5.6	NQ (<0.05)
NY/001-87-5013R	0.05	250-400	4	38.4-58.5	6.3-9.7	NQ - 8.1

Table cont'

Location/Study ID	lb a.i. /A[a]	Spray volume, GPA	No. of applications	Residue range, ppb (PHI in days) [b]		
				0	7	14
NJ/001-87-5014R	0.025	40	4	7.3-41.9	5.0-10.8	NQ - 7.8
NJ/001-87-5014R	0.05	40	4	30.0-51.0	7.4-15.1	5.5-24.3
NJ/001-87-5014R	0.025	250	4	13.7-22.0	NQ	NQ - 5.2
NJ/001-87-5014R	0.05	250	4	27.4-37.6	6.0-11.7	5.7-7.3
CA/001-87-5015R	0.025	40	4	22.4-32.2	8.5-14.8	9.2-13.6
CA/001-87-5015R	0.05	40	4	35.0-63.4	14.9-54.7	14.9-36.4
CA/001-87-5015R	0.025	400	4	9.2-17.9	NQ - 9.2	ND - 6.5
CA/001-87-5015R	0.05	400	4	26.2-40.5	7.4-11.4	9.5-28.9

[a] 1X rate: 0.025 lb a.i./A; 2X rate: 0.05 lb a.i./A; 0.05 lb a.i. is maximum/season

[b] Four samples analyzed for each PHI; ND: not detected, <0.02 ppm; NG: not quantitated, >0.02 ppm, <0.05 ppm; residue values represent Bl_a and its delta-8,9 isomer.

RESIDUE DATA 1988 FIELD TRIALS

Location/Study ID	lb a.i. /A[a]	Spray volume, GPA	No. of applications	Residue, ppb (PHI in days) [b]		
				0	7	14
OR/001-88-1009R	0.025	50-53	3	43.4	21.1, 25.5	---
OR/001-88-1010R	0.025	400	3	32.2	15.0, 20.5	---
WA/001-88-1018R	0.025	400	3	26.6	15.0, 15.2	---
WA/001-88-1024R	0.025	34-38	3	16.6	13.4, 15.3	---
NY/001-88-3019R	0.025	400	3	18.9	9.0, 16.2	---
PA/001-88-3020R	0.025	300	3	31.9	6.4, 7.6	---
CA/001-88-6047R	0.025	250	3	NQ	ND, ND	---

[a] 1X rate: 0.025 lb a.i./A; 2X rate: 0.05 lb a.i./A; 0.05 lb a.i. is maximum/season

[a] Only one sample analyzed once at day 0; one sample analyzed in duplicate at day 7; No data given for day 14; ND: not detected, <0.02 ppm; NQ: not quantitated, >0.02 ppm, <0.05 ppm; residue values represent Bl_a and its delta-8,9 isomer.

Meat, milk, poultry, and eggs

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.

The pear is not an animal feed item. Therefore, there is no resonable expectation of finite residues in livestock with this proposed use of avermectin B_1 on pears.

No changes in the tolerances are necessary at this time because the dietary burden of livestock will not be affected if a tolerance is established on pears.

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:6/7/91:RLoranger:6/11/91 H7509C:CBTS:JStokes:js:Rm 803A:CM#2:557-1439:6/20/91

J. Stokes 4/1/91

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Avermectin B_1

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. PP#9F3787

RCB Reviewer J. Stokes

Residue: Avermectin B_1 and its delta 8,9 isomer

Crop(s)	Limit (mg/kg)
pears	0.035

CANADIAN LIMITS:

[✓] No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

[✓] No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES: