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

NOV 26 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: PP#1F03973 and 1H05611. Abamectin (Avermectin B_1) for Use in/on Almonds, Walnuts, and Head Lettuce. Evaluation of Analytical Methodology and Residue Data. (MRIDs# 418225-00, 418225-01 (21 volumes), and 418225-02 (11 volumes). DP Barcodes# D163057 and D163060. CBTS# 7801 and 7802

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Merck Sharp and Dohme is requesting the establishment of permanent tolerances for abamectin (avermectin B_1) insecticide/miticide and its delta-8,9-isomer in/on the following commodities:

Commodity	Tolerance (ppm)
Almonds	0.005
Walnuts	0.005
Head Lettuce	0.05
Almond Hulls	0.10

All the tolerances established for avermectin B_1 are tolerances with an expiration date (expire 3/31/93). These include the RAC's cottonseed, citrus, cattle meat, cattle meat by-products, and milk at levels ranging from 0.005 to 0.01 ppm (40 CFR 180.449) and the food and feed additives citrus oil and citrus pulp, both at 0.10

ppm (40 CFR 185.300 and 186.300).

Tolerances are currently pending for use of abamectin on pears, strawberries, tomatoes, and celery.

CBRS has recommended in favor of Section 18 requests for abamectin in/on head lettuce and hops.

No registration standard has been prepared for abamectin.

Conclusions

1. Data in this petition were not generated by Craven Laboratories.

2. The manufacturing process of technical grade avermectin has been adequately described. No concern exists for any of the probable impurities. The formulation proposed for use on almonds, walnuts, and lettuce is AGRI-MEK 0.15 EC. All inerts in this formulation have been cleared under 40 CFR 180.1001.

3a. The proposed label for almonds and walnuts does not provide the dosage for full-coverage (dilute) sprays, applied to orchards, in the proper format. The dosage should be expressed as pounds active ingredient per 100 gallons of spray solution applied to runoff. Expressing the dosage in this form accounts for the variation in the quantity of active ingredient applied per acre as a result of the variation in tree size. To calculate this from the fluid ounces (or pounds active ingredient) per acre, the petitioner must provide data on the volume of spray per acre that was required (or would have been required if the trial was not performed to runoff) on the trees, at the time that the field trials were performed, to bring them to the point of runoff. This information will be required from the following, high-volume studies:

Almond
- 001-88-6028R
- 001-88-6035R
- 001-89-6020R

Walnut
- 001-88-6052R
- 001-89-6034R
- 001-88-6027R

Otherwise, full-coverage use must be dropped from the label. In addition, the volume of oil added will need to be expressed as percentage of the spray volume rather than as 1 gallon per acre (see Detailed Considerations, Proposed Use).

3b. The proposed label for almonds and walnuts does not vary the dosage for concentrated sprays, applied to orchards, based on tree size. CBTS recommends the following label change regarding

concentrated spraying of abamectin to tree nuts.

tree height (in feet)	fl.oz. AGRI-MEK/acre	lbs.ai./A.
less than 10	5 - 10	0.006 - 0.012
10 - 18	7.5 - 15	0.009 - 0.018
18 +	10 - 20	0.012 - 0.023

Apply the higher rate for control of heavier insect populations and/or European red mites. Do not apply more than 20 fl.oz./A./application or 60 fl.oz./A. in a 12 month period.

3c. The proposed label for application of AGRI-MEK 0.15EC to almonds and walnuts must be amended to specify the treatment interval between applications. The field residue data support a minimum treatment interval of 21 days (see Detailed Considerations, Proposed Use).

4. The nature of the residue in plants is adequately understood for the purposes of the proposed use on head lettuce, almonds, and walnuts. While the petitioner should be prepared to conduct additional plant metabolism studies on other crops to support future uses (especially if the use patterns differ significantly from those of cotton, celery, and citrus), CBTS concludes that the metabolism data are sufficient to support the proposed use on head lettuce, almonds, and walnuts. The residues of concern are avermectin B_1 and its delta-8,9-isomer (see Detailed Conclusions, Metabolism in Plants).

5. The nature of the residue in animals is adequately understood for the purposes of the proposed use on almonds. (Head lettuce and walnuts are not animal feed items). The residues of concern are avermectin B_1 and its delta-8,9-isomer. However, if in the future, registration is proposed on additional feed items such that the dietary burden to livestock is increased (see Detailed Considerations, Meat, Milk, Poultry, and Eggs), a new ruminant metabolism study with elevated feeding levels and use of a ^{14}C label may be required. Also, if the dietary burden is increased, the 24-hydroxymethyl metabolite may need to be regulated in meat and milk (see Detailed Conclusions, Metabolism in Animals).

6. CBTS concludes that the analytical methods for analysis of avermectin B_1 and its delta-8,9-isomer in/on head lettuce, walnuts, almonds, and almond hulls are adequate and suitable for enforcement purposes. In addition, avermectin has been subjected to testing under FDA multi-residue protocol methodology and cannot be recovered using any of the methods.

7a. No new storage stability studies were provided with this petition. The storage study data from previous submissions on citrus and tomatoes are not adequately representative of almond

nuts, walnuts, almond hulls, and head lettuce, nor are they adequate in duration. Therefore, at a minimum, the registrant must provide all currently available storage stability data on any RAC that show that avermectin B_1a, avermectin B_1b, and the delta-8,9-isomer of avermectin B_1a are stable over a period of at least 26.5 months. Otherwise, the registrant must provide data to show that avermectin B_1a, avermectin B_1b, and the delta-8,9-isomer of avermectin B_1a are stable in a representative leafy vegetable commodity (lettuce, celery, or spinach) over a period of 26.5 months and a representative tree nut commodity (almond, pecan, or English walnut) over a 14 month period. In addition, abamectin recoveries must be provided for almond hulls over a 23.5 month period.

In the future CBTS would like to see the petitioner perform storage stability on control samples from each crop group for which field residue data are provided. The storage conditions should reflect the storage conditions of the treated samples with respect to temperature, length of storage, containers, lighting, etc. Stability does not imply 100% recovery so, in order to get a maximum residue value, the residue data should still be corrected for storage study recovery (see Detailed Conclusions, Storage Stability).

7b. The registrant made no mention of the conditions under which the samples were held during transit from the field to the lab. This time period was as long as 18 days in transit. CBTS would like the registrant to comment on whether the samples were kept frozen during this time.

8. The registrant made no mention about whether or not the outer leaves of the lettuce heads were removed before processing and extraction. CBTS would like the registrant to clarify this point.

9. Pending the results from the requested storage stability study (see Detailed Conclusions, Storage Stability), the proposed almond nut, almond hull, walnut, and head lettuce tolerances may not be adequate. A final decision on the appropriate tolerance levels will be made after the storage stability data are submitted.

10. There are no feed items associated with the proposed use of abamectin on head lettuce, almond nuts, and walnuts and therefore these commodities should not create problems with secondary residues in meat, poultry, milk, and eggs. However, almond hulls are a feed item of ruminants. Pending the results from the requested storage stability study (see Detailed Considerations, Storage Stability), the established cattle meat and/or meat by-products tolerances may need to be revised. In any case, a new cattle fat tolerance of 0.015 ppm will need to be proposed in a revised Section F.

11. An International Residue Limit status sheet is appended to this review. No Codex, Canadian, or Mexican tolerances are established for avermectin. No compatibility problem exists between the proposed U.S. and Codex tolerances.

Recommendations

Until the deficiencies outlined in Conclusions 3a, 3b, 3c, 7a, 7b, 8, 9 and 10 are satisfactorily resolved, CBTS cannot recommend in favor of the proposed tolerances.

Note to P.M.: CBTS suggests that the petitioner be given a copy of this complete review. In addition, CBTS recommends that the label for application of AGRI-MEK 0.15 EC to citrus be revised to include a low volume (concentrated) rate based on tree height, as was included on previous label versions.

Detailed Considerations

Manufacturing and Formulation

Abamectin (avermectin B_1 or AVM B_1) is produced by a fermentation process using a strain of Streptomyces avermitilis. (This manufacturing process was reviewed in detail in L. Cheng's memo dated 5/1/86 reviewing EPA 618-OL). The technical product abamectin is a mixture of two homologs containing not less than 80% AVM B_1a and not greater than 20% AVM B_1b. These components differ by only one methylene unit at the 25-carbon position, wherein AVM B_1a contains a sec-butyl group and AVM B_1b contains an isopropyl group.

The technical material is about 95% AVM B_1 and contains about 0.5% of other AVMs of elucidated structures. The technical also contains about 1% of unidentified impurities related to the AVMs. TOX has no concern over these AVM-related impurities (see PP# 5G3287, memo of W. Dykstra, 3/3/86).

The formulation proposed for use on almonds, walnuts, and head lettuce is AGRI-MEK 0.15 EC, which is an emulsifiable concentrate (EC) containing 0.15 lbs active ingredient (ai.) per gallon (2.0 wt%). All inerts have been cleared for use under 40 CFR 180.1001 (see PP# 6G3320, memo of A. Smith, 6/23/86).

Proposed Use

Head Lettuce

For control of Liriomyza leafminers on head lettuce, apply AGRI-MEK 0.15 EC in a minimum of 10 gallons of water, using ground equipment only, at the rate of 8 to 16 fl.oz./A. (0.00938 to 0.0188 lb.ai./A.) depending on the extent of infestation. Apply

when adult flies are first observed and repeat applications at 7 day intervals or as necessary to maintain control, not to exceed 128 fl.oz./A. (0.15 lb.ai./A.) on a given head lettuce crop during its full cropping period. The minimum PHI is 7 days. Do not apply through any type of irrigation system. AGRI-MEK 0.15 EC may be used with or without a wetting agent (when used with a surfactant, Leaf Act®80A is recommended).

Almonds and Walnuts

For control of the following spider mites: two-spotted, Pacific, and strawberry, apply AGRI-MEK 0.15 EC at the rate of 10 to 20 fl.oz./A. (0.012 to 0.023 lb.ai./A.). For control of the European red mite, apply 20 fl.oz./A. (0.023 lb.ai./A.). Mix AGRI-MEK 0.15 EC with 1 gallon of paraffinic spray oil per acre and apply in a minimum of 40 gallons of water per acre using ground equipment only. Do not apply through any type of irrigation system. Apply product when mites first appear, and repeat application as needed to maintain control, not to exceed 20 fl.oz./A./application or 60 fl.oz./A./season (0.070 lb.ai./A./season). The minimum PHI is 21 days. Do not graze treated orchards.

The label states that AGRI-MEK 0.15 EC should be applied using conventional dilute or concentrate ground sprayers calibrated to deliver sufficient water for thorough coverage - the gallonage of spray will vary with the size and number of trees per acre and density of foliage. When using concentrate sprays, the amount of water is reduced but the amount of AGRI-MEK per acre should remain the same as for dilute sprays.

Comments and Recommendations (Almonds and Walnuts)

The proposed label does not have provisions for the different requirements when applying full-coverage or concentrated sprays to orchards. For full-coverage sprays to orchards, the dosage should be expressed as pounds of active ingredient per 100 gallons of spray solution applied to runoff. Expressing the dosage in this form accounts for the variation in the quantity of active ingredient applied per acre as a result of the variation in the size of trees. To calculate this from the fluid ounces (or pounds active ingredient) per acre, the petitioner must provide data on the volume of spray per acre that was required (or would have been required if the trial was not performed to runoff) on the trees, at the time that the field trials were performed, to bring them to the point of runoff. This information will be required from the following, high-volume studies:

Almond
- 001-88-6028R
- 001-88-6035R
- 001-89-6020R

Walnut
001-88-6052R
001-89-6034R
001-88-6027R

Otherwise, full-coverage use must be dropped from the label. In addition, the volume of oil added will need to be expressed as percentage of the spray volume rather than as 1 gallon per acre.

For concentrated orchard sprays, the amount of active ingredient applied per acre should be related to tree size. Almond trees grow about 12 to 18 inches a year[1] and come into commercial bearing in as little as 4 years (@ 500 lbs./A.)[2]. In the almond trials (almond hulls were the only tree nut RAC to show measurable residues), the shortest trees in any of the studies were at least 15 feet tall.

CBTS recommends the following label change regarding concentrated spraying of abamectin to tree nuts.

tree height (in feet)	fl.oz. AGRI-MEK/acre	lbs.ai./A.
less than 10	5 - 10	0.006 - 0.012
10 - 18	7.5 - 15	0.009 - 0.018
18 +	10 - 20	0.012 - 0.023

Apply the higher rate for control of heavier insect populations and/or European red mites. Do not apply more than 20 fl.oz./A./application or 60 fl.oz./A./12 month period.

The proposed label for application of AGRI-MEK 0.15EC to almonds and walnuts must be amended to specify the treatment interval between applications. In the six almond studies, 92% of the spray intervals were at 21 days or less. Actual spray intervals ranged from 20 to 22 days and 20 to 21 days between the first and second and second and third applications, respectively[3]. In the six walnut studies, 83% of the spray intervals were at 21 days or less. Actual spray intervals were all 21 days between the first and second applications, and ranged from 21 to 25 days between the second and third applications. The registrant should add the minimum treatment interval to the proposed label. Based on the field data, this interval should be no shorter than 21 days.

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[1] Modern Fruit Science, Childers, 1983.

[2] "An Analysis of Almond Production Costs in California", Agricultural Extension, University of California, 1973.

[3] In study 001-89-6020R, a fourth spraying was made 2 weeks after the third. The petitioner said that this modification was made since only 5% of the nuts were harvestable after the third spraying.

Nature of the Residue

Metabolism in Plants

No new plant metabolism data were submitted with this tolerance request. Metabolism data have been previously submitted on cottonseed, citrus, and celery (PP#'s 5G3500, 5G3287, and 8F3649, respectively). In addition, a report titled "Comparative Degradation of Avermectin B_1a in Cotton Leaf, Citrus Fruit, Celery, and In Vitro" was submitted in support of PP#9F3703 (reviewed by S. Willett in a memo from 12/15/89).

CBTS (formerly DEB) has previously concluded that the metabolism of abamectin in plants results in a complex mixture of residues. The majority of the terminal residue is composed of several unidentified polar degradates. The parent compound, its delta-8,9-isomer, and the alpha 8-OH degradate have been identified in plants, with only the parent and its delta-8,9-isomer each accounting for at least 10% of the total residue. To support the uses on cotton and citrus, the polar degradates generated on citrus (30X, 7 day PHI) and in vitro (30 hour sample)have been tested for toxicity and were found to be of no toxicological significance at the levels tested (see TOX memos 7080 and 7081 of W. Dykstra dated 3/15/89, and DEB memo of F. Boyd concerning 8F3592 dated 6/21/89).

The proposed use on almonds and walnuts specifies multiple applications, up to 6, and a maximum application rate of 60 fl. oz./A./season (0.070 lb.ai./A./season). The proposed use on head lettuce specifies multiple applications, up to 16, and a maximum application rate of 128 fl.oz./A./season (0.15 lb.ai./A./season). Previously, the metabolism components have been examined from radio-labeled abamectin on celery (10 applications at 7 day intervals for a total equivalent of 1.0 lb.ai./A./season), radio-labeled abamectin on cotton (3 applications at 50 to 89 day intervals for a total equivalent of 0.60 lb./A./season), and exaggerated application rates to citrus (30X, 2.25 lb.ai./A.). The available metabolism data on cotton, celery, and citrus represent a wide enough range of crop matrices, growth modes, and use rates to conclude that it is unlikely that application of abamectin to lettuce, almonds, and walnuts will form new compounds that have not previously been produced and subjected to toxicity testing. While the petitioner should be prepared to conduct additional plant metabolism studies on other crops to support future uses (especially if the use patterns differ significantly from those of cotton, celery, and citrus), CBTS concludes that the metabolism data are sufficient to support the proposed use on head lettuce, almonds, and walnuts. The residues of concern are the parent and its delta-8,9-isomer.

Metabolism in Animals

No additional animal metabolism data were submitted with this petition.

Although usually regarded as supplemental data by Chemistry Branch, rat metabolism data were submitted and reviewed in conjunction with PP#'s 4F3065, 5F3287, and 7G3468. The major metabolite identified in the avermectin-fed rats was the 3"-desmethyl compound with the 24-hydroxymethyl metabolite as a minor component. In addition, the pathway of the delta-8,9-isomer (a plant metabolite) of avermectin B_1 in rats was investigated and found to be analogous to avermectin (The corresponding 24-hydroxymethyl and 3"-desmethyl isomers were found.).

Data from a goat metabolism study were previously reviewed in PP#7G3468 (memo of L. Cheng, 2/11/87). These data were summarized by S. Willett in her memo of 12/15/89 regarding PP#9F3703. Three groups of two goats were fed 0.005, 0.05, and 1.0 mg. ^{3}H-avermectin B_1a per day for 10 consecutive days. A total of 99% of the radio-labeled dose was excreted in the feces consisting of the following compounds: about 70% as B_1a, 20% as the 24-hydroxymethyl metabolite, and 5% as the 3"-desmethyl metabolite. No accumulation in tissues or milk was found at these levels. The residue levels that were found in goat tissues and organs from the 1 mg/day dose are summarized in Table 1.

Table 1

Residue Levels in Goat Tissues

	Total B_1a Equivalents (in ppb)	
Tissue	Goat 1	Goat 2
liver	98	16
kidney	23	4.8
peripheral fat	50	7.6
omental fat	49	6.8
leg muscle	7.6	1.7
loin muscle	9.9	1.2

In the goat tissues, the undegraded avermectin B_1a accounted for the majority (37-99%) of the residue, with the 24-hydroxymethyl compound being the major metabolite (<1 to 43%). Residues in milk of goats dosed at the 1 mg/day level rose to a maximum of 4.7 ppb at day 7 with a composition consisting of 79 to 92% B_1a and 2 to 11%

of the 24-hydroxymethyl metabolite. In summary, avermectin B_1a, 3"-desmethyl avermectin B_1a (major metabolite in rats), and/or 24-hydroxymethyl avermectin B_1a (major metabolite in goats) were the major components in animal tissues.

The high level dose in the goat study (1 mg/goat/day) is 20 times higher than the expected residue to be fed ruminants from citrus pulp (see memo of F. Boyd dated 6/21/89 concerning 8F3592). Based on the additional dietary burden of tomato pomace and almond hulls (raising the dose to 0.077 ppm - see Detailed Considerations, Meat, Milk, Poultry, and Eggs), the residue levels are still within the range (about 10X lower) used in setting the dose concentrations in the goat metabolism study. The ^{3}H-goat study is still considered sufficiently representative for determining the fate of avermectin residues in the ruminant from the 0.077 ppm feeding level. However, if, in the future, registration is proposed on additional feed items such that the dietary burden to cattle is increased (see Detailed Considerations, Meat, Milk, Poultry, and Eggs), a new ruminant metabolism study with elevated feeding levels and the use of a ^{14}C-label may be required.

Based on feeding cattle a diet of cottonseed, citrus pulp, tomato pomace, and almond hulls bearing residues of abamectin, the residues of concern in animals are the parent compound (B_1a), and its delta-8,9-isomer. If the tolerances for residues in meat and milk need to be raised at some future time due to registration of abamectin on additional feed items, the 24-hydroxymethyl metabolite may need to be included in the tolerance expression and appropriate enforcement methods developed (see F. Boyd memo of 6/21/89).

Analytical Method

The petitioner has submitted three different methods for the analysis of avermectin B_1 and its delta-8,9-isomer in the various RACs. These methods vary slightly in the extraction steps but the derivitization and analysis is performed in a similar way. These methods quantitate both avermectin B_1a and its delta-8,9-isomer (a photodegradate) as a single component. In addition, these methods quantitate B_1b, and by analogy, its delta-8,9-isomer as a second component.

Method 8900 - "HPLC-Fluorescence Determination For Avermectin B_1 and its Delta-8,9-Isomer in Pecan, Walnut, and Almond Nutmeat"

This method was developed and validated by Merck Sharp and Dohme Laboratories.

Extraction:

Residues of avermectin B_1 and its delta-8,9-isomer are extracted from 5 gram nut meat homogenates by blending with methanol. The methanol extract is made aqueous and washed with isooctane to remove excess oil. The aqueous methanol solution is passed through an octyl (C_8) column, loading the avermectins onto the column. The eluent is discarded and the C_8 column is piggybacked onto an aminopropyl (NH_2) column. The avermectins are eluted from the C_8 column with a small volume of methanol and filtered through the NH_2 column. The sample, in methanol, is then split and evaporated to dryness.

Derivatization and Analysis:

The dried residue is converted to a fluorescent derivative by reaction with a mixture of N,N-dimethylformamide trifluroacetic anhydride and 1-methylimidazole [Reagent A(1)] for 1 hour at 30°C, followed by reaction with methanolic ammonium hydroxide in chloroform and passed through a silica column for separation of the derivatized residue from derivatization reagents. The eluent is taken to dryness and reconstituted in methanol. The derivatized residue is determined by reversed-phase liquid chromatography with fluorescence detection. Since derivatization of the delta-8,9-isomer produces the same derivative as avermectin B_1, the derivatized residue quantitated represents the sum of avermectin and its delta-8,9-isomer.

Recoveries:

For almond nutmeat homogenates, recoveries of avermectin B_1a averaged 88% (RSD=7.6%, n=7) for fortifications ranging from 5.0 to 70.0 ng/g. Avermectin B_1b recoveries averaged 90% (RSD=3.9%, n=3) for homogenates fortified at 5.2 ng/g. At fortifications ranging from 5.0 to 70.0 ng/g, recoveries of the delta-8,9-isomer of B_1a averaged 83% (RSD=8.9%, n=9).

For walnut nutmeat homogenates, recoveries of avermectin B_1a averaged 95% (RSD=5.6%, n=7) for fortifications ranging from 5.0 to 70.0 ng/g. Avermectin B_1b recoveries averaged 107% (RSD=5.7%, n=3) for homogenates fortified at 5.2 ng/g. At fortifications ranging from 5.0 to 70.0 ng/g, recoveries of the delta-8,9-isomer of B_1a averaged 89% (RSD=3.8%, n=9).

Method 8950 - "HPLC-Fluorescence Determination For Avermectin B_1 and its Delta-8,9-Isomer in Almond Nut Hulls"

The original method was developed by Merck but modified and validated by Analytical Development Corporation (ADC), Colorado Springs, Colorado.

Extraction:

Residues of avermectin B_1 and its delta-8,9-isomer are extracted from 5 gram nut hull homogenates by blending with acetonitrile. The acetonitrile extract is washed with hexane. The acetonitrile is concentrated by evaporation and diluted with water. The aqueous acetonitrile in the presence of salt is extracted three times with hexane, removing the avermectins from the aqueous acetonitrile. The hexane extracts are combined and loaded onto an aminopropyl (NH_2) column which retains the avermectins. The hexane eluent is discarded. The column is washed with hexane, toluene, and methylene chloride and the eluent is evaporated to dryness and reconstituted in acetonitrile. The sample is then split and evaporated to dryness.

Derivatization and Analysis:

See Method 8900.

Recoveries:

For almond hull homogenates, recoveries of avermectin B_1a averaged 85% (RSD=9.2%, n=15) for fortifications ranging from 5.0 to 70.0 ng/g. Avermectin B_1b recoveries averaged 91% (RSD=6.4%, n=6) for homogenates fortified at 5.2 ng/g. At fortifications ranging from 5.0 to 70.0 ng/g, recoveries of the delta-8,9-isomer of B_1a averaged 77% (RSD=5.8%, n=17).

Method 10001 Rev. 2 - "HPLC-Fluorescence Determination For Avermectin B_1 and its Delta-8,9-Isomer in Celery and Lettuce"

Method 10001 was originally developed and validated by Merck Sharp and Dohme Labs for the determination of abamectin and its delta-8,9-isomer in celery. Merck contracted Hazleton Laboratories in Madison, Wisconsin to modify and validate this method to extend the application to lettuce (Method 10001 rev. 1). Method 10001 rev. 2 was written to combine the lettuce and celery methods into one method.

Extraction:

Residues of avermectin B_1 and its delta-8,9-isomer are extracted from the ground celery or lettuce by blending with acetonitrile. The extract is filtered and made more aqueous by the addition of water. The aqueous solution is passed through a C_8 column, loading the avermectins onto the column. The eluent is discarded and the avermectins are eluted with a small volume of acetonitrile. The acetonitrile is concentrated and water is added to the acetonitrile. The aqueous acetonitrile is extracted with hexane three times, removing the avermectins from the aqueous

acetonitrile. The hexane extracts are combined and loaded onto an aminopropyl column, which retains the avermectins. The hexane eluent is discarded. The column is washed with hexane, toluene, and methylene chloride and the avermectins are eluted with 50:50 acetone/methylene chloride. This eluent is evaporated to dryness.

Derivatization and Analysis:

See Method 8900.

Recoveries:

For lettuce homogenates, recoveries of avermectin B_1a averaged 91% (RSD=11.0%, n=15) for fortifications ranging from 5.0 to 71.1 ng/g. Avermectin B_1b recoveries averaged 92% (RSD=2.2%, n=5) for homogenates fortified at 5.3 ng/g. At fortifications ranging from 5.0 to 70.6 ng/g, recoveries of the delta-8,9-isomer of B_1a averaged 82% (RSD=11.0%, n=15).

Comments and Recommendations

Based on these methods, residues of avermectin B_1a/delta-8,9-isomer below 2 ng/g are non-detectable (reported as ND). The peak representing avermectin B_1a/delta-8,9-residues between 2 and 5 ng/g is identified but not quantitated (reported as NQ) and the peak for residues above 5 ng/g is identified and quantitated. Since avermectin B_1b is at most 20% (usually less than 10%) of the active ingredient, its residue levels are generally less than the quantitation limit (5 ng/g) or the detection limit (2 ng/g). The peak representing avermectin B_1b is identified but not quantitated when the residue level is between 2 and 5 ng/g. Residues of avermectin B_1b above 5 ng/g are identified and quantitated in the same manner as the avermectin B_1a/delta-8,9-isomer, using the avermectin B_1a standard curve for quantitation.

In general, it is inappropriate to quantitate one compound using the standard for another. The petitioner states that because it has been found that a standard curve of B_1b will produce a slightly higher slope than that of B_1a, attempts to quantitate avermectin B_1b from B_1a will, at worst, result in an overestimation of actual B_1b residues. In addition, the contribution of B_1b to the total B_1 is very small (typically about 10%). Therefore, CBTS does not believe that this questionable practice adversely affects the total residue values, in this case.

Method validation of analytical methodology to determine residues of avermectin B_1a, its delta-8,9-isomer, and B_1b in plant and animal commodities have been conducted by the agency. Merck Method 1009R3 (citrus methodology) and Method 32A (animal commodities) were determined to be adequate for enforcement purposes (see method evaluation reports of F. Boyd dated 9/2/88,

and S. Willett dated 9/11/89). The methods were recently sent to the FDA for publication in PAM II. A method for cottonseed has also been submitted as a letter method (see memo of S. Willett, 9/21/89). The methodology has not yet been published in PAM II but may be obtained from PIB/FOD. An additional validation of the method used for pears has been requested (see memo of J. Stokes, 3/22/91).

Avermectin has been tested using methodology described in PAM I, multi-residue method protocol A, which is the only applicable protocol. Avermectin is not recovered using the multi-residue methodology.

CBTS concludes that the analytical methods for analysis of avermectin B_1 and its delta-8,9-isomer in/on head lettuce, walnuts, almonds, and almond hulls are adequate and suitable for enforcement purposes.

Residue Data

Storage Stability

No storage stability data were provided with this petition. Previous storage stability data were provided with citrus (see memo of F. Boyd, 6/21/89 concerning 8F3592) and tomatoes (see memos of S. Willett addressing 9F3703 (12/15/89) and 1E3943 (4/22/91)). Various citrus were spiked at 10 and 50 ppb avermectin B_1 and 10 ppb for the delta-8,9-isomer of B_1a. DEB concluded that recoveries in the spiked, stored samples demonstrate no detectable loss of any of the three chemical entities during 12 months of freezer storage.

In the tomato petition, tomato samples were spiked at levels of 10 and 50 ppb of B_1 and 10 ppb of the delta-8,9-isomer of B_1a. Initially, the sample recoveries were low and/or inconsistent (25-77%) using Merck Method 9003, even with the freshly spiked (Day 0) samples. The samples were reanalyzed at a later date using Method 8002 and the 15 month old samples showed adequate recoveries for all three compounds (82-107%). Additionally, tomatoes from residue trials conducted in the U.S., originally analyzed using Method 9003, were reanalyzed after up to 28 months of storage using Method 8002. Recoveries varied from 78 to 88%. However, CBTS does not believe that this is an adequate storage stability test since the initial and 28 month samples were analyzed by different methods; more than 1 variable was being evaluated.

The storage study data from previous submissions on citrus and tomatoes are not adequately representative of almond nuts, walnuts, almond hulls, and head lettuce, nor are they adequate in duration. Therefore, at a minimum, the registrant must provide all currently available storage stability data on any RAC that show that avermectin B_1a, avermectin B_1b, and the delta-8,9-isomer of

avermectin B_1a are stable over a period of at least 26.5 months. Otherwise, the registrant must provide data to show that avermectin B_1a, avermectin B_1b, and the delta-8,9-isomer of avermectin B_1a are stable in a representative leafy vegetable commodity (lettuce, celery, or spinach) over a period of 26.5 months and a representative tree nut commodity (almond, pecan, or English walnut) over a 14 month period. In addition, abamectin recoveries must be provided for almond hulls over a 23.5 month period.

In the future CBTS would like to see the petitioner perform storage stability on control samples from each crop group for which field residue data are provided. The storage conditions should reflect the storage conditions of the treated samples with respect to temperature, length of storage, containers, lighting, etc. The best way to assure this is to spike controls at the same time that the field residue samples are harvested, and then store them in the same freezer during the same time period. Stability does not imply 100% recovery so, in order to get a maximum residue value, the residue data should still be corrected for storage study recovery.

In addition, the registrant made no mention of the conditions under which the samples were held during transit from the field to the lab. This time period was as long as 18 days in transit. CBTS would like the registrant to comment on whether the samples were kept frozen during this time.

Magnitude of the Residue

Almonds

Since over 99% of all domestic almonds are grown in California[4], the 6 trial sites supporting tolerances for almond nuts and hulls were conducted in that state in 1988 and 1989. Two different almond varieties were represented, including Nonpareil, the most important commercial variety. Three of the trial sites were conducted using dilute sprays (between 350 and 400 gal./A.) and three using concentrate sprays (between 17 and 20 gal./A.). AGRI-MEK 0.15 EC was applied by ground equipment at 0.025 (1X) and 0.05 lb.ai./A. (2X) three times[5] at approximately 21 day intervals. In all trials, 1 gallon per acre of paraffinic oil was mixed with the abamectin solution. The nuts were harvested at various intervals, including at the proposed 21 day PHI. The residue analyses were performed for both almond nuts and the animal feed item almond hulls. The methods used (Merck methods 8900 and 8950) quantitate both the B_1a/delta-8,9-isomer and B_1b/delta-8,9-isomer.

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[4]Census of Agriculture, 1987, vol 1, part 51, "United States Summary and State Data", table 28.

[5] In one study, a fourth application was made.

None of the almond nuts analyzed, that were sprayed at the 1X rate, had detectable residues (<2 ug/g).

The results of the almond hull analyses are summarized in Table 2.

Table 2

Residue Summary of Avermectin B_1 and Its Delta-8,9-Isomer in/on Almond Hulls

							Maximum Total Residues in PPB (uncorrected for method and storage recoveries)		
Trial Site	Study	Year	Variety	Spray Volume Applied (gal/A)	Use Level (lb.ai./A.)	PHI (days)	B_1a	B_1b	Total*
Fresno, CA	001-88-6028R	1988	Nonpareil	400	0.025 (1X)	0	16.1	ND	17
					0.05 (2X)	0	47.6	NQ	52
					0.025 (1X)	21	ND	ND	2
					0.05 (2X)	21	NQ	ND	5
Berenda, CA	001-88-6032R	1988	Nonpareil	20	0.025 (1X)	0	266	29.8	296
					0.05 (2X)	0	676	71.6	748
					0.025 (1X)	3	95.2	10.4	106
					0.05 (2X)	3	334	38.5	372
					0.025 (1X)	7	83.0	8.7	92
					0.05 (2X)	7	232	25.6	258
					0.025 (1X)	14	47.4	5.1	52
					0.05 (2X)	14	194	21.7	216
					0.025 (1X)	21	42.2	NQ	46
					0.05 (2X)	21	166	17.5	184
Hughson, CA	001-88-6034R	1988	Nonpareil	17.7 to 18.9	0.025 (1X)	0	347	35.1	382
					0.05 (2X)	0	1096	104	1200
					0.025 (1X)	21	70.0	6.7	77
					0.05 (2X)	21	157	16.0	173
Hughson, CA	001-88-6035R	1988	Nonpareil	350	0.025 (1X)	0	201	22.3	223
					0.05 (2X)	0	619	67.8	687
					0.025 (1X)	21	53.4	5.9	59
					0.05 (2X)	21	216	23.2	239

Trial Site	Study	Year	Variety	Spray Volume Applied (gal/A)	Use Level (lb.ai./A.)	PHI (days)	Maximum Total Residues in PPB (uncorrected for method and storage recoveries)		
							B_1a	B_1b	Total*
Suisun, CA	001-89-6019R	1989	Mission	20	0.025 (1X)	0	108	29.5	138
					0.025 (1X)	14	17.5	NQ	22
					0.025 (1X)	21	15.6	ND	17
Wasco, CA	001-89-6020R	1989	Mission	400	0.025 (1X)	0	204	26.5	2070
					0.025 (1X)	14	52.4	7.4	60
					0.025 (1X)	21	28.3	NQ	32

ND represents values less than 2.0 ppb.
NQ represents values greater than or equal to 2 but less than 5.
* For totals, a numerical value of 1 was used for ND and 4 for NQ. Values were rounded to the nearest whole number.

Walnuts

Approximately 98% of the English walnuts grown in the U.S. come from California[6]. Therefore, in support of this petition, 6 trial sites were chosen in California [3 using dilute sprays (300 to 400 gal./A.) and 3 using concentrate sprays (20 gal./A.)] in 1988 and 1989. Five different walnut varieties were represented in the trials. AGRI-MEK 0.15 EC was applied by ground equipment at 0.025 (1X) and 0.05 lb.ai./A. (2X), three times at approximately 21 day intervals. In all trials, 1 gallon of paraffinic oil per acre was mixed with the abamectin and applied to the trees. The nuts were all harvested at a 14 day PHI (21 day PHI is proposed on the label). The walnut nuts were analyzed by Merck method 8900, which quantitates both the B_1a/delta-8,9-isomer and B_1b/delta-8,9-isomer.

None of the walnut samples analyzed had detectable residues (<2 ug/g).

Lettuce

Eleven residue trials were conducted in 5 states in 1987 through 1990. These sites are representative of the diversity of growing areas for head lettuce; these 5 states account for over 93% of U.S. head lettuce production[7]. Nine different varieties of head

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[6]Census of Agriculture, 1987, vol 1, part 51, "United States Summary and State Data", table 28.

[7]Census of Agriculture, 1987, vol 1, part 51, "United States Summary and State Data", table 27.

lettuce were represented. Various spray volumes were used (between 10 and 100 gallons per acre), and use rates [0.02 (1X) and 0.04 lb.ai./A. (2X)], both with and without Leaf Act® 80A surfactant. In the various trials, 6 to 10 applications were made at 3 to 9 days apart. The lettuce was harvested at various intervals, including the proposed 7 day PHI (at one trial site, harvest was made at a 5 day PHI). The method used (10001 rev 2) quantitates both the B_1a/delta-8,9-isomer and B_1b/delta-8,9-isomer.

The results of the lettuce analyses are summarized in Table 3.

Table 3

Residue Summary of Avermectin B_1 and Its Delta-8,9-Isomer in/on Head Lettuce

							Maximum Total Residues in PPB (uncorrected for method and storage recoveries)		
Trial Site	Study	Year	Variety	Spray Volume Applied (gal/A)	Use Level (lb.ai./A.)	PHI (days)	B_1a	B_1b	Total*
Holtsville, CA	001-87-1001R	1987	Iceberg	100	0.02 (1X)	0	150	13.7	164
					0.02 (1X)▲	0	213	22.1	235
					0.02 (1X)	5	29.6	NQ	34
					0.02 (1X)▲	5	28.5	NQ	32
Marcellus, MI	001-87-5027R	1987	Ithaca	50	0.02 (1X)	0	13.8	ND	15
					0.02 (1X)▲	0	19.4	ND	20
					0.04 (2X)	0	36.1	NQ	40
					0.04 (2X)▲	0	69.3	7.0	76
					0.02 (1X)	5	NQ	ND	5
					0.02 (1X)▲	5	7.6	ND	9
					0.04 (2X)	5	5.3	ND	6
					0.04 (2X)▲	5	16.8	ND	18
					0.02 (1X)	7	5.3	ND	6
					0.02 (1X)▲	7	6.6	ND	8
					0.04 (2X)	7	6.0	ND	7
					0.04 (2X)▲	7	11.5	ND	12
Calipatria, CA	001-88-1066R	1988	Winter Haven	10	0.02 (1X)	0	102	10.1	112

Trial Site	Study	Year	Variety	Spray Volume Applied (gal/A)	Use Level (lb.ai./A.)	PHI (days)	Maximum Total Residues in PPB (uncorrected for method and storage recoveries)		
							B_1a	B_1b	Total*
					0.02 (1X)▲	0	68.3	8.8	77
					0.04 (2X)	0	194	21.0	215
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	NQ	ND	5
Mecca, CA	001-89-1002R	1989	Autumn Gold	50	0.02 (1X)	0	6.5	ND	8
					0.02 (1X)▲	0	44.7	NQ	49
					0.04 (2X)	0	70.2	9.1	79
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	ND	ND	2
Scottsdale, AZ	001-89-1043R	1989	Ramrod	37	0.02 (1X)	0	138	17.2	155
					0.02 (1X)▲	0	113	14.1	127
					0.04 (2X)	0	125	15.1	140
					0.02 (1X)	7	25.2	NQ	29
					0.02 (1X)▲	7	20.9	NQ	25
					0.04 (2X)	7	28.6	NQ	33
Yuma, AZ	001-89-1048R	1989	Empire	10	0.02 (1X)	0	41.5	5.2	47
					0.02 (1X)▲	0	36.5	NQ	40
					0.04 (2X)	0	84.8	10.6	95
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	NQ	ND	5
Zellwood, FL	001-89-0046R	1989	Green Lakes	40	0.02 (1X)	0	6.1	ND	7
					0.02 (1X)▲	0	18.5	ND	20
					0.04 (2X)	0	61.0	7.2	68
					0.02 (1X)	7	ND	ND	2

Trial Site	Study	Year	Variety	Spray Volume Applied (gal/A)	Use Level (lb.ai./A.)	PHI (days)	Maximum Total Residues in PPB (uncorrected for method and storage recoveries)		
							B_1a	B_1b	Total*
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	ND	ND	2
Zellwood, FL	001-89-0047R	1989	Green Lakes	30	0.02 (1X)	0	9.4	ND	10
					0.02 (1X)▲	0	51.0	6.1	57
					0.04 (2X)	0	29.2	7.2	36
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	ND	ND	2
Watsonville, CA	001-89-6055R	1989	Salinas M.T.	40	0.02 (1X)	0	45.3	5.7	51
					0.02 (1X)▲	0	59.2	6.4	66
					0.04 (2X)	0	175	20.8	196
					0.02 (1X)	7	5.6	ND	7
					0.02 (1X)▲	7	21.5	NQ	26
					0.04 (2X)	7	28.1	NQ	32
Five Points, CA	001-89-6052R	1989	Empire	30	0.02 (1X)	0	11.2	ND	12
					0.02 (1X)▲	0	11.7	ND	13
					0.04 (2X)	0	NQ	ND	5
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2
					0.04 (2X)	7	ND	ND	2
Montrose, CO	001-90-1008R	1990	Green Duchess	20	0.02 (1X)	0	ND	ND	2
					0.02 (1X)▲	0	15.6	ND	17
					0.02 (1X)	7	ND	ND	2
					0.02 (1X)▲	7	ND	ND	2

▲ - spray mixture included between 4 and 8 fl.oz./A. of Leaf Act®80A.
ND represents values less than 2.0 ppb.
NQ represents values greater than or equal to 2 but less than 5.
* For totals, a numerical value of 1 was used for ND and 4 for NQ. Values were rounded to the nearest whole number.

Comments

Almonds and Walnuts

None of the almond nut and walnut residue values at the 1X rate and 21 day PHI were above 2 ppb. Unless the requested storage study shows poor recoveries (see section on Storage Stability), the proposed tolerance of 0.005 ppm should be adequate to cover residues of abamectin on almond nuts and walnuts when applied according to the proposed (by CBTS) label directions. CBTS cannot make a final ruling at this time.

On almond hulls, the largest residue value found was 0.077 ppm when AGRI-MEK was applied at the 1X rate and 21 day PHI. Pending the results from the requested storage stability study (see Detailed Consideration, Storage Stability), the proposed almond hull tolerance of 0.10 ppm may not be adequate to cover residues of abamectin when applied according to the proposed (by CBTS) label directions. A revised Section F may be needed pending the results.

Lettuce

On samples bearing measurable residues, 14 out of 19 times the addition of surfactant increased the residue values. At the 1X rate and proper PHI, the largest total residue value found was 0.034. Pending the results from the requested storage stability study (see Detailed Consideration, Storage Stability), the proposed head lettuce tolerance of 0.050 ppm may not be adequate to cover residues of abamectin when applied according to the proposed label directions. A revised Section F may be needed pending the results.

The registrant made no mention about whether or not the outer leaves of the lettuce heads were removed before processing and extraction. CBTS would like the registrant to clarify this point.

Meat, Milk, Poultry, and Eggs

Almond hulls are an animal feed item. They can comprise up to 25% of the diet of cattle. The results from a hypothetical diet for beef and dairy cattle based on a maximum use of treated cotton, citrus, tomato[8], and almond feed items are summarized in Table 4.

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[8] The use of abamectin on tomatoes is pending. However as the calculations show, the use or non-use of the pending tomato tolerance requires a cattle fat tolerance and does not affect the level of the current meat/meat by-product tolerances.

Table 4

Maximum AVM Residues in Cattle from Various Crops

Ingredients	AVM Residues in Ingredients (ppm)	% in Cattle Diet		Maximum AVM Residues Fed (in ppm)	
		Beef	Dairy	Beef	Dairy
almond hulls	0.10	25	25	0.025	0.025
Citrus pulp	0.10	33	33	0.033	0.033
tomato pomace	0.07	25	25	0.018	0.018
cottonseed	0.005	17	17	0.00085	0.00085
Total	-	100	100	0.077	0.077

The proposed tolerance on almond hulls may change based on the storage stability results (see section on Storage Stability). However even a large change in this value is unlikely to impact the proposed cattle fat tolerance and the established meat/meat by-product tolerance.

Using the feed factor (dose) for dairy cattle at 0.077 ppm, the potential maximum residues of AVM B_1 in meat and milk can be estimated. The 28 day feeding study submitted with PP#7G3468 (see memo of L. Cheng, 2/11/87) was performed on dairy cattle at levels of 10, 30, and 100 ppb of AVM residues in the diet. The levels are summarized in Table 5

Table 5

AVM Levels in Dairy Cattle Tissues

Dose (ppb)	AVM Levels in Various Tissues and Organs (ppb)			
	Liver	Muscle	Fat	Kidney
10	3-4	1-2	2	1-2
30	5-8	2	4-6	2
100	18-20	2	10-14	4-5

Therefore, from feeding 77 ppb of residues, maximum residues of 15 ppb in meat, meat by-products, or fat would be expected. At the highest feeding level of 100 ppb, the maximum residue in milk was 4 ppb at Day 14 with only 1 ppb found at Day 28. Therefore, the

maximum residues expected in milk from feeding 77 ppb AVM are 3 ppb.

Tolerances with an expiration date of 3/31/93 are established for avermectin B_1 and its delta-8,9-isomer in cattle meat and meat by-products at 0.020 ppm, and in milk at 0.005 ppm. These levels are adequate to cover the increased dietary burden of almond hulls in the diet of cattle. However, the previous tolerance on cattle fat at 0.010 ppm that expired on 5/1/89 will need to be increased and extended. A new Section F proposing a tolerance of 0.015 ppm on cattle fat would seem appropriate based on the data provided.

Other Considerations

An International Residue Limit status sheet is appended to this review. No Codex, Canadian, or Mexican tolerances are established for avermectin. No compatibility problem exists between the proposed U.S. and Codex tolerances.

Attachment I - International Residue Limit Status sheet

cc: PP#1F03973 and 1H05611, RF, circu., E. Haeberer (section head), G.J. Herndon, C. Furlow (PIB/FOD), PM#15, TOX II, SF.

RDI: Section Head: E. Haeberer: 11/13/91, Branch Senior Scientist: R.A. Loranger: 11/21/91.

H7509C: CBTS: G.J. Herndon: 557-4379: CM#2, Rm. 814A: 10/30/91.

F. Reeves 10/1/91.

Attachment: Page 1 of 1

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Avermectin B_1 (Abamectin)

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. 1F03973 and 1H05611

DEB Reviewer Herndon

Residue: parent + Δ8,9 isomer

Crop(s)	Limit (mg/kg)
Head lettuce	0.05
Walnuts	0.005
Almonds	0.005
Almond hulls	0.10

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 1989