PP#4354

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: PP#4F04345 and FAP#4H05693. Abamectin (Avermectin B_1) for Use in/on Apples. Evaluation of Analytical Methodology and Residue Data.
No MRIDs#
DP Barcodes# D201328 and D201333
CBTS# 13512 and 13513

From: G. Jeffrey Herndon, Chemist
Tolerance Petition Section II
Chemistry Branch I - Tolerance Support
Health Effects Division (7509C)

G. Jeffrey Herndon

Through: Edward Zager, Acting Chief
Chemistry Branch I - Tolerance Support
Health Effects Division (7509C)

Edward Zager

To: George LaRocca/Linda Arrington, PM# 13
Insecticide-Rodenticide Branch
Registration Division (7505C)

and

Jane Smith, Acting Head
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

Merck and Co., Inc. 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)
Apples (RAC)	0.02
Apples, wet pomace	0.10

Tolerances have been established for avermectin B_1 on various RACs, processed commodities, and animal feeds (40 CFR 180.449, 185.300, and 186.300).

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Previously, Merck was granted a Section 5 registration (EUP) and temporary tolerance for use of avermectin on apples (see memos of J.B. Stokes dated 3/22/91 and 2/3/94 concerning PP#1G3930).

No registration standard has been prepared for abamectin.

Conclusions

1. Residue data in this petition were analyzed by Merck Research 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 apples is AGRI-MEK 0.15 EC (EPA Reg.# 618-98). All inerts in this formulation have been cleared under 40 CFR 180.1001.

3. In the review of proposed label for use of avermectin on tree nuts (PP#1F3973, memo of G.J. Herndon dated 11/26/91), CBTS noted that, for concentrated orchard sprays, the amount of active ingredient applied should be proportional to tree size. This issue was also discussed in meetings with Merck on 9/8/94 and 2/28/95. Merck has submitted a draft proposal to the Agency that addresses this issue generically for all their tree crops (phone conversation with L. Grosso of Merck). At the present time, CBTS has not received this proposal, and will defer the acceptance of the proposed apple label until we have reviewed the draft protocol.

4. The nature of the residue in plants is adequately understood for the purposes of the proposed use on apples. The residues of concern are avermectin B_1 and its delta-8,9-isomer.

5. The nature of the residue in animals is adequately understood for the purposes of the proposed use on apples. The residues of concern are avermectin B_1 and its delta-8,9-isomer.

6a. Merck Method 8000 rev. 4 for analysis of avermectin B_1 and its delta-8,9-isomer in/on apples and pears appears to be adequate and suitable for enforcement purposes. The method has been independently validated and is currently being validated on pears at the EPA Beltsville lab (see memo of G.J. Herndon dated 3/27/95 concerning PP#9F3787). Pending successful validation on pears, CBTS will deem Method 8000 rev. 4 acceptable for enforcing the proposed tolerance of 0.020 ppm on apples. However, until the EPA lab validation on pears is completed, CBTS cannot make any final conclusions concerning the adequacy of the proposed enforcement method.

6b. Merck Method 92-1 appears to be adequate for analyzing residues of avermectin in apple processed commodities.

6c. Avermectin has been subjected to testing under FDA multi-residue protocol methodology and cannot be recovered using any of the methods.

7. The storage stability data previously submitted on pears should be representative and sufficient in duration to insure the stability of avermectin residues in the apple field residue samples.

8. Pending Merck's response to Conclusions 3 and 10, and the resolution of Conclusion 6a, the following tolerances, which are proposed in the Section F, should be adequate to cover residues from the proposed use:

Commodity	Tolerance (ppm)
apples (RAC)	0.02
apple pomace (wet)	0.10

9. Based on the data submitted with this apple petition (PP#1G3930 and PP#4F4345) and previous pear petition (PP#9F3787), Merck can receive a pome fruit crop group tolerance without generating any more field trial residue data. Merck should be advised of this and asked if they desire the pome fruit crop group tolerance.

10. The established tolerances for cattle meat (0.02 ppm) and cattle meat by-products (0.02 ppm) are adequate to cover the increased dietary burden from the addition of the feed item apple pomace. However, CBTS reiterates (from the 11/26/91 memo of G.J. Herndon concerning PP#1F3973) that a cattle fat tolerance will need to be proposed (no cattle fat tolerance is currently established). In the memo of 11/26/91, CBTS recommended a level of 0.015 ppm, which should still be adequate based on additional feed items (see Acute section under Meat, Meat Byproducts, and Fat of this memo).

11. Pending Merck's response to Conclusions 3 and 10, and the resolution of Conclusion 6a, CBTS will recommend that the following residue values be used in the acute and chronic dietary risk assessment for avermectin.

Acute and Chronic Residue Values to be Used in the Dietary Risk Assessment of Avermectin

DRES entry	Entry for **ACUTE** Risk Assessment (ppm)	Entry for **CHRONIC** Risk Assessment (ppm)
apples, dried	0.088	0.013
apples, fresh	0.020	0.003
apples, juice	0.0015	0.0002
beef fat	0.014	0.006
beef lean	0.002	0.002
beef kidney	0.005	0.002
beef liver	0.020	0.008
beef dried	0.002	0.002
beef meat byproducts	0.020	0.008
milk sugar	0.001	0.00025
milk fat	0.004	0.001
milk, non-fat solids	0.004	0.001

12. Avermectin tolerances on various commodities are under consideration by Codex, but have not been officially adopted. No Canadian or Mexican tolerances are established for avermectin and therefore no compatibility problem exists between the proposed U.S. and Codex tolerances.

Recommendations

Until the deficiencies outlined in Conclusions 3, 6a, and 10 are satisfactorily resolved, CBTS cannot recommend in favor of the proposed tolerances.

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 apples 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

For control of tentiform leafminers and spider mites on apples, apply AGRI-MEK 0.15 EC (EPA Reg.# 618-98) using ground equipment only, at the rate of 10 to 20 fl.oz./A. (0.012 to 0.023 lb.ai./A.) depending on the extent of infestation. AGRI-MEK 0.15 EC should be applied in conjunction with 1 gallon of paraffinic crop oil per acre. Apply when established thresholds have been reached, but do not make more than 2 applications per growing season and do not exceed 40 fl.oz./A./growing season (0.046 lb.ai./A./season). Do not apply in less than 40 gallons of spray volume (water + oil) per acre. Do not apply through any type of irrigation system. The minimum PHI is 28 days.

Comments

In the review of proposed label for use of avermectin on tree nuts (PP#1F3973, memo of G.J. Herndon dated 11/26/91), CBTS noted that, for concentrated orchard sprays, the amount of active ingredient applied should be proportional to tree size. This issue was also discussed in meetings with Merck on 9/8/94 and 2/28/95. Merck has submitted a draft proposal to the Agency that addresses this issue generically for all their tree crops (phone conversation with L. Grosso of Merck). At the present time, CBTS has not received this proposal, and will defer the acceptance of the proposed apple label until we have reviewed the draft protocol.

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 apples specifies up to 2 applications and a maximum application rate of 40 fl.oz./A./season (0.046 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 apples 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 apples. The residues of concern are the parent compound (avermectin B_1a and B_1b) and its delta-8,9-isomer.

Metabolism in Animals

No additional animal metabolism data were submitted with this petition. 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. ^3H-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 almond hulls, tomato pomace, and apple pomace (raising the dose to 0.092 ppm - see Detailed Considerations under Milk and Meat, Meat Byproducts, and Fat), the residue levels are still within the range (about 10X lower) used in setting the dose concentrations in the goat metabolism study. The ^3H-goat study is still considered sufficiently representative for determining the fate of avermectin residues in the ruminant from the 0.092 ppm feeding level. However, if, in the future, registration is proposed on additional feed items such that the dietary burden to cattle is increased, 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, almond hulls, and apple pomace 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

No new analytical method was submitted with the current petition. Method 8000 for analyzing residues of avermectin B_1 in apples was submitted and reviewed in conjunction with PP#1G3930 (see memos of J.B. Stokes dated 3/22/91 and 2/3/94). This method is essentially the same as Merck Method 8000 rev. 4 (MRID# 426922-01), which is intended to be used on both apples and pears, and is currently at Beltsville being validated down to 0.02 ppm on pears (see memo of G.J. Herndon dated 10/21/94 concerning PP#9F3787). Based on the method, residues of avermectin B_1a/delta-8,9-isomer below 1 ng/g are non-detectable (reported as ND). The peak representing avermectin B_1a/delta-8,9-residues between 1 and 2 ng/g is identified but not quantitated (reported as NQ) and the peak for residues above 2 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 (2 ng/g) or the detection limit (1 ng/g). The peak representing avermectin B_1b is identified but not quantitated when the residue level is between 1 and 2 ng/g. Residues of avermectin B_1b above 2 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.

Validation data for apples were provided in conjunction with the method validation of Method 8000 rev. 4 on pears (MRID# 426922-01, see memo of G.J. Herndon dated 10/21/94 concerning PP#9F3787).

The method for processed apple fractions (Method 92-1) is similar to Merck Method 8000. It differs in that it employs a quick derivatization, similar to the Merck tomato processed fractions method (Method 9003R01). The method was validated to the same 2 ng/g limit of quantitation on apple processed commodities (juice, sauce, and pomace) that Method 8000 on the apple RAC was validated. Method 92-1 was reviewed in the memo of J.B. Stokes dated 2/3/94.

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.

Provided that the method passes Beltsville lab validation on pears at 0.02 ppm, Method 8000 rev. 4 should also be adequate for enforcing a 0.02 ppm tolerance on apples (RAC).

Residue Data

Storage Stability

No storage stability data were provided with this petition. In conjunction with PP#1F3973/1H5611 (see memo 5/19/94), Merck referenced previously submitted storage stability data on various crops. The composite crops/recoveries are shown in Table 2.

Table 2

Storage Stability Recoveries for Abamectin Residues in Various Crop Matrices (stored at ≤ -10°C)

Matrix	Length of Frozen Storage (months)	Fortification Level (ppm) and Compound	Method Recovery at Longest Time Interval#	Storage Stability Recovery at Longest Time Interval*
celery	24	0.010 - B1a	70%	79%
		0.206 - B1a		70%
		0.015 - B1b		87%
		0.010 - Δ8,9 isomer		70%
pears	35	0.010 - B1a	95%	84%
		0.071 - B1a		86%
		0.005 - B1b		72%
		0.010 - Δ8,9 isomer		94%
strawberries	24	0.010 - B1a	105%	98%
		0.071 - B1a		102%
		0.005 - B1b		109%
		0.010 - Δ8,9 isomer		94%
tomatoes	24	0.010 - B1a	87%	88%
		0.051 - B1a		86%
		0.004 - B1b		90%
		0.009 - Δ8,9 isomer		74%
cottonseed	14	0.010 - B1a	73%	58%
whole oranges	29	0.010 - B1a	86%	89%
		0.052 - B1a		89%
		0.004 - B1b		95%
		0.010 - Δ8,9 isomer		84%
whole grapefruit	29	0.010 -B1a	96%	92%
		0.052 - B1a		82%
		0.004 - B1b		104%
		0.010 - Δ8,9 isomer		85%
whole lemons	29	0.010 - B1a	84%	86%
		0.052 - B1a		86%
		0.004 - B1b		98%
		0.010 - Δ8,9 isomer		83%
orange peel	52	0.025 - B1a	87%	67%
grapefruit peel	47	0.005 - B1a	unk.	85%
		0.025 - B1a		70%
lemon peel	47	0.005 - B1a	88%	93%
		0.025 - B1a		79%

- fresh fortification

* - uncorrected for method recovery

The storage stability data previously submitted on pears should be representative and sufficient in duration to insure the stability of avermectin residues in the apple field residue samples.

Magnitude of the Residue

Tolerance (Acute Risk Assessment)

Handling of Non-Quantifiable (NQ) and Non-Detectable Residues in Setting the Tolerance (Acute Risk Assessment)

The matrix and methodology allow for a limit of quantitation (LOQ) of 2 ppb and a limit of detection (LOD) of 1 ppb. In Table 3, the designations NQ and ND are used. NQ refers to samples that were not quantifiable (1 - 2 ppb). Since these samples exhibited a clear peak in the retention time window of the compound of interest, albeit below the LOQ (2 ppb), the concentration of avermectin residues in these samples will be estimated as 2 ppb for the purposes of tolerances (and therefore, acute risk assessment). ND refers to samples that were not detected (< 1 ppb). A value of 1 ppb will be assigned to these samples for the purposes of tolerances (and therefore, acute risk assessment).

The field trial data that were submitted with PP#1G3930 (see memo of J.B. Stokes dated 2/3/94), that reflect a 1X rate and 28 day PHI, and the assumptions outlined above, are summarized below in Table 3.

Table 3

Residue Summary of Avermectin in/on Apples

Study ID	Avermectin Residues (ppb)		
	B_1a	B_1b	Total
001-90-5016R	2.8	ND (1)	3.8
	NQ (2)	ND (1)	3
	NQ (2)	ND (1)	3
	ND (1)	ND (1)	2
001-90-5018R	5.9	NQ (2)	7.9
	4.1	ND (1)	5.1
	3.1	ND (1)	4.1
	2.7	ND (1)	3.7
001-91-1021R	NQ (2)	ND (1)	3
	ND (1)	ND (1)	2
001-91-1023R	2.9	ND (1)	3.9
	2.0	ND (1)	3
001-91-1024R	2.4	ND (1)	3.4
	NQ (2)	ND (1)	3
001-91-6016R	10	NQ (2)	12
	8.1	ND (1)	9.1
001-91-6024R	ND (1)	ND (1)	2
	ND (1)	ND (1)	2
001-91-3000R	6.9	ND (1)	7.9
	4.5	ND (1)	5.5
001-92-0026R	2.6	ND (1)	3.6
	NQ (2)	ND (1)	3
001-92-0027R	NQ (2)	ND (1)	3
	ND (1)	ND (1)	2
001-92-1014R	ND (1)	ND (1)	2
	ND (1)	ND (1)	2
001-92-1018R	NQ (2)	ND (1)	3
	ND (1)	ND (1)	2
001-92-3020R	3.7	ND (1)	4.7
	NQ (2)	ND (1)	3
001-92-6012R	3.3	ND (1)	4.3
	ND (1)	ND (1)	2

Based on the data in Table 3 (in particular, trial 001-91-6016R), CBTS recommends that **a tolerance value of 0.020 ppm should be established for residues of avermectin on apple**, which is what Merck has proposed in their Section F.

Chronic Risk Assessment

Handling of Non-Quantifiable (NQ) and Non-Detectable Residues in the Chronic Risk Assessment

The matrix and methodology allow for a limit of quantitation (LOQ) of 2 ppb and a limit of detection (LOD) of 1 ppb. In Table 4, the designations NQ and ND will be used. NQ refers to samples that were not quantifiable (1 - 2 ppb). Since these samples exhibited a clear peak in the retention time window of the compound of interest, albeit below the LOQ (2 ppb), the concentration of avermectin residues in these samples will be estimated as 2 ppb. ND refers to samples that were not detected (< 1 ppb). For the purposes of chronic risk assessment, a value of 1 ppb (½ X 2 ppb) will be used.

If B_1a is ND

Abamectin (avermectin 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% avermectin B_1a and not greater than 20% avermectin B_1b. These components differ by only one methylene unit at the 25-carbon position, wherein avermectin B_1a contains a sec-butyl group and avermectin B_1b contains an isopropyl group. Based on the residue data reviewed to date, the metabolism in plants does not seem to alter this ratio of B_1a to B_1b (at least 4 to 1). Therefore, for the purposes of chronic risk assessment, for those samples which exhibit non-detectable (ND) B_1a residues, a value of ¼ of ND will be used to estimate B_1b residue levels. Since a value of 0.5 ppb will be used for ND B_1a residues, a value of 0.125 ppb (¼ X 0.5 ppb) will be used to estimate the B_1b residue contribution of those samples.

The field trial data that were submitted with PP#1G3930 (see memo of J.B. Stokes dated 2/3/94), that reflect a 1X rate and 28 day PHI, and the assumptions outlined above, are summarized below in Table 4.

Table 4

Residue Summary of Avermectin in/on Apples

Study ID	Avermectin Residues (ppb)		
	B_1a	B_1b	Total
001-90-5016R	2.8	ND (0.5)	3.3
	NQ (2)	ND (0.5)	2.5
	NQ (2)	ND (0.5)	2.5
	ND (0.5)	ND (0.125)	0.63
001-90-5018R	5.9	NQ (2)	7.9
	4.1	ND (0.5)	4.6
	3.1	ND (0.5)	3.6
	2.7	ND (0.5)	3.2
001-91-1021R	NQ (2)	ND (0.5)	2.5
	ND (0.5)	ND (0.125)	0.63
001-91-1023R	2.9	ND (0.5)	3.4
	2.0	ND (0.5)	2.5
001-91-1024R	2.4	ND (0.5)	2.9
	NQ (2)	ND (0.5)	2.5
001-91-6016R	10	NQ (2)	12
	8.1	ND (0.5)	8.6
001-91-6024R	ND (0.5)	ND (0.125)	0.63
	ND (0.5)	ND (0.125)	0.63
001-91-3000R	6.9	ND (0.5)	7.4
	4.5	ND (0.5)	5.0
001-92-0026R	2.6	ND (0.5)	3.1
	NQ (2)	ND (0.5)	2.5
001-92-0027R	NQ (2)	ND (0.5)	2.5
	ND (0.5)	ND (0.125)	0.63
001-92-1014R	ND (0.5)	ND (0.125)	0.63
	ND (0.5)	ND (0.125)	0.63
001-92-1018R	NQ (2)	ND (0.5)	2.5
	ND (0.5)	ND (0.125)	0.63
001-92-3020R	3.7	ND (0.5)	4.2
	NQ (2)	ND (0.5)	2.5
001-92-6012R	3.3	ND (0.5)	3.8
	ND (0.5)	ND (0.125)	0.63

From the data above, a mean of 3.2 ppb was determined (32 entries for a total of 101.17 ppb). **CBTS recommends that a value of 0.003 ppm be used as the chronic anticipated residue for apples.**

Based on the data submitted with this apple petition (PP#1G3930 and PP#4F4345) and previous pear petition (PP#9F3787), Merck can receive a pome fruit crop group tolerance without

generating any more field trial residue data. Merck should be advised of this and asked if they desire the pome fruit crop group tolerance.

Processing Studies

A apple processing study was submitted in conjunction with PP#1G3930. The data provided in Table 5 were taken from samples collected at a 7 day PHI. For the residue values that are listed as ND, an assumption has been made that the actual residue values are ½ of the limit of detection (0.5 ppb), and the concentration of B_1b can only be a maximum of 25% of the concentration of B_1a.

Table 5

Results of an Avermectin Apple Processing Study

	avermectin residues (ppb)			
fraction	B_1a	B_1b	Total	concentration factor
whole, unwashed apples	8.1	ND (0.5)	8.6	-
peel/cored apples	ND (0.5)	ND (0.125)	0.63	0.073
wet pomace	40	4.3	44.3	5.15
dry pomace (non-rehydrated)	140	15	155	18.0
dry pomace (rehydrated)	120	13	133	15.5
raw juice	ND (0.5)	ND (0.125)	0.63	0.073
clarified juice	ND (0.5)	ND (0.125)	0.63	0.073
applesauce	ND (0.5)	ND (0.125)	0.63	0.073

Data available to CBTS indicate that apples processed into juice yield about 80% juice on a weight basis[1]. CBTS can conclude that the concentration factor for wet apple pomace listed in Table 5 (5.15) is close to that of theoretical (20% of the apple weight is pomace, so the concentration factor is about 5). This indicates that the avermectin residues in/on apples are almost completely surface residues (also substantiated by the non-detectable residues in peeled/cored apples). Therefore, the non-detectable residues in apple juice and applesauce make sense and the resulting concentration factors of 0.073 may actually be exaggerated.

Based on the concentration factors discussed above, the following residue values should be used for estimating the acute anticipated residues for the following processed apple commodities.

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[1] Processed Apple Products, Donald Downing, Van Nostrand Reinhold, N.Y., 1989.

DRES entries
apple
whole tolerance on RAC = 0.02 ppm
juice 0.073 X RAC = 0.0015 ppm
dried 4.4 (provided by DRES) X RAC = 0.088 ppm
Animal feeds
apple pomace (wet) tolerance = 0.10 ppm (5 X RAC)

Since residues of avermectin concentrate in apple pomace, a tolerance of 0.10 ppm is needed, which is in agreement with what Merck proposed in their Section F.

Based on the concentration factors discussed above, the following residue values should be used for estimating the chronic anticipated residues for the following processed apple commodities.

DRES entries
CAR = chronic anticipated residue of the RAC = 0.003 ppm
whole CAR = 0.003 ppm
juice 0.073 X CAR = 0.0002 ppm
dried 4.4 (provided by DRES) X CAR = 0.013 ppm
Animal feeds
apple pomace (wet) = 5 X CAR = 0.015 ppm

These data are summarized in Table 6

Table 6

Acute and Chronic Residue Values to be Used in the Dietary Risk Assessment of Avermectin

DRES entry	Entry for **ACUTE** Risk Assessment (ppm)	Entry for **CHRONIC** Risk Assessment (ppm)
apples, dried	0.088	0.013
apples, fresh	0.020	0.003
apples, juice	0.0015	0.0002

Milk

Acute

The established tolerance for residues of avermectin in milk is 0.005 ppm.

Based on a production figure of 50 pounds of milk per day, a realistic cow diet was established based on our in-house Spartan Dairy Ration Evaluator program. The residue levels used for the feed items in Table 7 are taken from those developed for acutes for apple pomace in this memo, in combination with those developed for

other feed items developed in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Table 7

Maximum Avermectin Residues in Dairy Cattle from Various Crops

Ingredients	pounds of dry matter	pounds (as fed)	% in diet (based on dry matter)	% in diet (as fed)	Maximum Avermectin Residues (ppb)	
					In Feed Items	In the Diet (normalized to 100% total of all feed items)
alfalfa hay	13	14.8	32.5%	26.62%	N/A	N/A
almond hulls	6	6.7	15%	12.05%	100	12.0
cotton hulls	6	6.6	15%	11.87%	5	0.594
cottonseed meal	3	3.2	7.5%	5.76%	5	0.288
tomato pomace (dried)	4	4.3	10%	7.73%	70	5.41
apple pomace (wet)	8	20	20%	35.97%	100	36.0
TOTAL	40	55.6	100%	100%	N/A	54

Using the feed factor (dose) for dairy cattle at 54 ppb, the potential maximum residues of avermectin B_1 in milk can be estimated. The 28 day feeding study submitted with PP#7G3468 (see memo of L. Cheng dated 2/11/87) was performed on dairy cattle at levels of 10, 30, and 100 ppb of avermectin residues in the diet. The milk levels are summarized in Table 8.

Table 8

Avermectin Levels in Cows Milk from a 28 Day Feeding Study

	Avermectin Residues (ng/mL) in Various Milk Samples During the 28 Day Dosing Period at 3 Feeding Levels		
Day	10 ppb	30 ppb	100 ppb
1	ND	ND	ND
2	ND	ND	ND - 1 ppb (ave. = 0.5 ppb)
3	ND	ND	ND - 1 ppb (ave. = 0.5 ppb)
5	ND	ND - 1 ppb (ave. = 0.5 ppb)	ND - 1 ppb (ave. = 0.5 ppb)
7	ND	ND	1 - 2 ppb (ave. = 1.3 ppb)
14	ND	ND	1 - 4 ppb (ave. = 2.3 ppb)
28	ND	ND	1 ppb (ave. = 1 ppb)
Average	0.25 ppb	0.36 ppb	0.91 ppb

ND - not detected down to the lower limit that adequate method recoveries were achieved (0.5 ppb). For the purposes of the risk assessment, an ND value of ½ X 0.5 ppb, or 0.25 ppb will be used.

Since milk from various cows is mixed and composited, an average residue value during the 28 day dosing period from the 100 ppb feeding level was chosen to best correspond to the cow consuming a theoretical 54 ppb of residue in its diet. Therefore,

from feeding 54 ppb of residues, residues in milk would be estimated to be 1 ppb. **CBTS recommends that a value of 0.001 ppm be used as the acute anticipated residue for milk.** Avermectin is intermediate in polarity (very soluble in chloroform, not as soluble in hexane or water). The normal concentration factors that would be applied to the DRES entries for non-fat milk solids and milk fat are 8X. Based on its solubility, for risk assessment purposes, CBTS will assume that ½ of the residue will go into each fraction (concentration factors of 4X for each). **Therefore, the following residue values should be used for estimating the acute anticipated residues for the following DRES milk entries.**

CAMR - calculated acute milk residue = 0.001 ppm

milk fat 4 X CAMR = 0.004 ppm
non-fat milk solids 4 X CAMR = 0.004 ppm
milk sugar CAMR = 0.001 ppm

These values are unchanged from the ones recommended in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Chronic

Based on a production figure of 50 pounds of milk per day, a realistic cow diet was established based on our in-house Spartan Dairy Ration Evaluator program. The residue levels used for the feed items in Table 9 are taken from those developed for chronics for apple pomace in this memo, in combination with those developed for other feed items developed in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Table 9

Maximum Avermectin Residues in Dairy Cattle from Various Crops

Ingredients	pounds of dry matter	pounds (as fed)	% in diet (based on dry matter)	% in diet (as fed)	Maximum Avermectin Residues (ppb)	
					In Feed Items	In the Diet (normalized to 100% total of all feed items)
alfalfa hay	13	14.8	32.5%	26.62%	N/A	N/A
almond hulls	6	6.7	15%	12.05%	39.0	4.70
cotton hulls	6	6.6	15%	11.87%	0.5	0.0593
cottonseed meal	3	3.2	7.5%	5.76%	0.5	0.0288
tomato pomace (dried)	4	4.3	10%	7.73%	11	0.850
apple pomace (wet)	8	20	20%	35.97%	15	5.40
TOTAL	40	55.6	100%	100%	N/A	6.6

Using the feed factor (dose) for dairy cattle at 6.6 ppb, the potential maximum residues of avermectin B_1 in milk can be estimated. Data from the same 28 day feeding study that was used

for the acute dietary risk assessment (see Table 8 above) was used. An average residue value from the 10 ppb feeding level was chosen to best correspond to the cow consuming a theoretical 6.6 ppb of residue in its diet. Therefore, from feeding 6.6 ppb of residues, residues in milk would be estimated to be 0.25 ppb. **CBTS recommends that a value of 0.00025 ppm be used as the chronic anticipated residue for milk.** Avermectin is intermediate in polarity (very soluble in chloroform, not as soluble in hexane or water). The normal concentration factors that would be applied to the DRES entries for non-fat milk solids and milk fat are 8X. Based on its solubility, for risk assessment purposes, CBTS will assume that ½ of the residue will go into each fraction (concentration factors of 4X for each). **Therefore, the following residue values should be used for estimating the chronic anticipated residues for the following DRES milk entries.**

CCMR - calculated acute milk residue = 0.00025 ppm

milk fat	**4 X CCMR =**	**0.001 ppm**
non-fat milk solids	**4 X CCMR =**	**0.001 ppm**
milk sugar	**CCMR =**	**0.00025 ppm**

These values are unchanged from the ones recommended in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Meat, Meat Byproducts, and Fat

Apple pomace and other crops which are allowed to have avermectin residues are not routinely fed to poultry. Therefore, this section only addresses the meat, meat byproducts, and fat of beef cattle.

Acute

Based on a intake figure of 1.8 pounds of crude protein and 18 pounds of dry matter, a realistic diet for an 800 pound steer was established based on our in-house Spartan Dairy Ration Evaluator program. The residue levels used for the feed items in Table 10 are taken from those developed for acutes for apple pomace in this memo, in combination with those developed for other feed items developed in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Table 10

Maximum Avermectin Residues in Beef Cattle from Various Crops

Ingredients	pounds of dry matter	pounds (as fed)	% in diet (based on dry matter)	% in diet (as fed)	Maximum Avermectin Residues (ppb)	
					In Feed Items	In the Diet (normalized to 100% total of all feed items)
almond hulls	2.0	2.2	11.0%	7.18%	100	7.18
cottonseed	0.3	0.33	1.6%	1.08%	5	0.054
fescue hay	4.0	4.4	21.8%	14.36%	N/A	N/A
tomato pomace (dried)	4.5	4.9	24.6%	16.00%	70	22.86
apple pomace (wet)	7.5	18.8	41%	61.38%	100	61.38
TOTAL	18.3	30.63	100%	100%	N/A	92

Using the feed factor (dose) for dairy cattle at 92 ppb, the potential maximum residues of avermectin in meat, fat, and meat byproducts can be estimated. The 28 day feeding study submitted with PP#7G3468 (see memo of L. Cheng dated 2/11/87) was performed on dairy cattle at levels of 10, 30, and 100 ppb of avermectin residues in the diet. The levels are summarized in Table 11.

Table 11

Avermectin Levels in Dairy Cattle Tissues from a 28 Day Feeding Study

Dose (ppb)	Avermectin 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

The residue levels from the 100 ppb feeding were chosen to best represent the residue levels from a theoretical 92 ppb diet. Based on this, **the following residue values should be used for estimating the acute anticipated residues for the following DRES beef entries.**

beef

fat	**0.014 ppm**	
lean	**0.002 ppm**	
kidney	**0.005 ppm**	
liver	**0.020 ppm**	
dried	**0.002 ppm**	**(same as lean)**
byproducts	**0.020 ppm**	**(taken from liver)**

These values are unchanged from the ones recommended in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

The established tolerances for cattle meat (0.02 ppm) and cattle meat by-products (0.02 ppm) are adequate to cover the increased dietary burden from the addition of the feed item apple pomace. However, CBTS reiterates (from the 11/26/91 memo of G.J. Herndon concerning PP#1F3973) that a cattle fat tolerance will need to be proposed (no cattle fat tolerance is currently established). In the memo of 11/26/91, CBTS recommended a level of 0.015 ppm, which should still be adequate based on additional feed items.

Chronic

Based on a intake figure of 1.8 pounds of crude protein and 18 pounds of dry matter, a realistic diet for an 800 pound steer was established based on our in-house Spartan Dairy Ration Evaluator program. The residue levels used for the feed items in Table 12 are taken from those developed for chronics for apple pomace in this memo, in combination with those developed for other feed items developed in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Table 12

Maximum Avermectin Residues in Beef Cattle from Various Crops

Ingredients	pounds of dry matter	pounds (as fed)	% in diet (based on dry matter)	% in diet (as fed)	Maximum Avermectin Residues (ppb)	
					In Feed Items	In the Diet (normalized to 100% total of all feed items)
almond hulls	2.0	2.2	11.0%	7.18%	39	2.80
cottonseed	0.3	0.33	1.6%	1.08%	0.5	0.0054
fescue hay	4.0	4.4	21.8%	14.36%	N/A	N/A
tomato pomace (dried)	4.5	4.9	24.6%	16.00%	11	1.76
citrus pulp (dried)	7.5	18.8	41.0%	61.38%	15	9.21
TOTAL	18.3	30.63	100%	100.5%	N/A	14

Using the feed factor (dose) for dairy cattle at 14 ppb, the potential maximum residues of avermectin B^1 in meat, fat, and meat byproducts can be estimated. Data from the same 28 day feeding study that was used for the acute dietary risk assessment (see Table 11 above) was used. The residue levels from the 30 ppb feeding were chosen to best represent the residue levels from a theoretical 14 ppb diet. Based on this, **the following residue values should be used for estimating the chronic anticipated residues for the following DRES beef entries.**

beef

fat	**0.006 ppm**	
lean	**0.002 ppm**	
kidney	**0.002 ppm**	
liver	**0.008 ppm**	
dried	**0.002 ppm**	**(DRES uses beef lean value)**
byproducts	**0.008 ppm**	**(taken from liver)**

These values are unchanged from the ones recommended in the memo of G.J. Herndon dated 12/21/94 concerning PP#9F3787.

Other Considerations

Avermectin tolerances on various commodities are under consideration by Codex, but have not been officially adopted. No Canadian or Mexican tolerances are established for avermectin and therefore no compatibility problem exists between the proposed U.S. and Codex tolerances.

cc: PP#4F04354, RF, circu., E. Haeberer (section head), G.J. Herndon.

RDI: Section Head: E. Haeberer: 5/1/95,
Branch Senior Scientist: R. Loranger: 5/1/95,
Acting Branch Chief: E. Zager: 5/1/95.

H7509C: CBTS: G.J. Herndon: 305-6362: CM#2, Rm. 804C: 4/25/95.