PP#8F3592/FAP#8H5550

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

JUN 21 1989
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#8F3592/FAP#8H5550 - Abamectin (Avermectin B_1) on Citrus - Evaluation of Petitioner Response (9/16/88) to the DEB Review of 4/25/88. MRID No. 408315-01 and DEB Nos. 4457 and 4458.

FROM: V. Frank Boyd, Ph.D., Chemist
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THRU: Richard D. Schmitt, Ph.D., Acting Chief
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Richard D Schmitt

TO: George LaRocca, P.M. 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

and

Edwin Budd/William Dykstra
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Background

Merck Sharp and Dohme has submitted a response to the latest DEB review pertaining to proposed use of avermectin on citrus (M. Kovacs, PP#8F3592/FAP#8H5550, April 25, 1988).

The first permanent tolerance has recently been established for avermectin in cottonseed at 0.005 ppm for avermectin B_1, and its 8,9-delta isomer. No tolerances in meat and milk have been established. A proposed tolerance of 0.035 ppm in celery is pending.

Deficiencies Remaining to be Resolved:

The following residue chemistry deficiencies pertaining to PP#8F3592/FAP#8H5550 remain outstanding:

- O A new section F must be submitted proposing new tolerance levels as follows:

Citrus, whole fruit	0.02 ppm
Cattle meat and meat byproducts	0.02 ppm
Milk	0.005 ppm
Dried citrus pulp	0.10 ppm
Citrus oil	0.10 ppm

- O The petitioner must submit a revised enforcement method writeup for inclusion in the Pesticide Analytical Manual, Vol. II. Method 1009 No. 2 (for whole fruit) must be revised to include the alternate cleanup procedures specified in Method 1004R02 for analysis of dried pulp and oil.

Conclusions:

1. The qualitative nature of the residue in citrus (and cotton) is adequately understood. The residues of concern are avermectin B_1 and its delta-8,9-isomer.

2. For purposes of the proposed use on citrus and the previously approved use on cotton, the qualitative nature of the residue in ruminants is adequately understood. 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, a new goat 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. For a more detailed discussion of issues pertaining to the nature of the residue in ruminants, refer to DEB's conclusions regarding deficiencies 3d and 3e under "Detailed Considerations."

3. Adequate enforcement methodology is available for monitoring avermectin residues in whole citrus (Method 1009R02), citrus pulp and oil (Method 1004R02) and meat and milk (Method 32A). However, the petitioner must submit a revision of Method 1009R02 that includes the specific cleanup steps specified in Method 1004R02 for analysis of citrus pulp and oil. This revised method and method 32A for meat and milk will be sent to FDA for inclusion in the PAM, Vol. II.

4. Sufficient field residue, processing, and ruminant feeding study data have been submitted to determine that the tolerances originally proposed for citrus fruit, oil and pulp and cattle meat, meat byproducts and milk are too low. A new section F with increased levels as specified above under "Deficiencies Remaining to be Resolved" must be submitted.

Recommendations:

DEB could recommend for the following tolerances provided the deficiencies cited above under "Deficiencies Remaining to be Resolved" are resolved and the TOX Branch concurs:

Citrus, whole fruit	0.02 ppm
Cattle meat and meat byproducts	0.02 ppm
Milk	0.005 ppm
Dried citrus pulp	0.10 ppm
Citrus oil	0.10 ppm

Detailed Considerations:

The deficiencies cited in M. Kovacs 4/25/88 memo are restated below in numerical order followed by the petitioner's 9/16/88 response and DEB's current conclusions.

Deficiency 2a:

In a revised Section B/label under Remark a/ "Apply in 500-2000 gallons" should be changed to "Apply in 500-1000 gallons" to keep the total dosage applied to 20 fl. oz. AGRIMEC per acre per application or 0.025 lb ai/A/application.

Petitioner's Response to Deficiency 2a:

Label change - "Apply in 500-1000 gallons".

DEB's Response and Conclusions to Deficiency 2a:

The petitioner has effected the recommended label change, and Deficiency 2a is considered satisfied.

Deficiency 2b:

In a revised Section B/label, the petitioner will need to specify the treatment interval and timing of applications during the growing season.

Petitioner's Response to Deficiency 2b:

Most growers will use only one (summer) application per season; however in some cases two or three applications may be needed to control mites from postbloom in the spring to the fall application for the following season's protection. The corrected labeling states: "Apply when mite pressure appears in spring, summer or fall. ...Do not apply within 7 days of harvest. ...Do not apply more than 60 fl. oz. per acre in any 12 month period."

DEB's Response and Conclusions on Deficiency 2b:

The labeling is considered to be as specific as possible, and therefore is adequate. Deficiency 2b is considered to be satisfied.

Deficiency 3a:

RCB concludes that the residues of concern on citrus consist of AVM B_1 and its delta-8,9 isomer provided that TB expresses no concern regarding the presence of unidentified polar degradates which may comprise up to 70 percent of the total terminal residue. TB's opinion in turn regarding the toxicological significance of these polar degradates is predicated upon their favorable review and evaluation of the teratology tests and the Ames test conducted on these polar degradates when submitted by the petitioner.

Petitioner's Response to Deficiency 3a:

The residues of concern consist of abamectin and its delta 8,9-isomer. The polar fraction of the terminal residue has been tested toxicologically. Two sources of polar material have been tested: thin film photolysis - Ames Test, CF-1 Mouse teratology, Citrus derived - CF-1 Mouse teratology. Full reports of the former have been previously submitted, full reports of the latter test will be submitted 9/88. The above tests are negative and show the polar fraction is not of toxicological concern.

DEB's Response and Conclusions to Deficiency 3a:

Toxicology Branch I on March 15, 1989, issued two memorandums: #007080 (Additional Toxicology Studies with Delta-8,9-Isomer and Polar Degradates) and #007081 (Mouse Teratology Study with Citrus-Derived Polar Degradates of Abamectin). It was concluded in these evaluations that the polar degradates derived from citrus were of no toxicological significance. Therefore, the residues of concern for Abamectin are concluded to be the parent compound and its delta-8,9-isomer in citrus and cotton. Deficiency 3a is satisfied.

Deficiency 3b:

If TB's evaluation of the teratology tests and Ames tests described in 2a above is unfavorable, wherein the identities of the polar degradates are needed, then RCB must conclude that the nature of the residue in plants is not adequately understood. The petitioner must then characterize the subject polar degradates as comprising a significant portion of the total toxic residue. Furthermore, the tolerance expression would probably need to be revised to include these polar degradates. Accordingly, this would require validated enforcement analytical methodology and additional residue data on citrus generated utilizing this methodology.

Petitioner's Response to Deficiency 3b:

The petitioner refers to the response in 3a above.

DEB's Response and Conclusions to Deficiency 3b:

Based on DEB's conclusion in 3a, above, it is concluded that Deficiency 3b is satisfied.

Deficiency 3c:

If Toxicology Branch considerations permit, RCB concludes that metabolism studies using AVM B_1b are not needed. Studies using AVM B_1a adequately reflect the metabolism of the technical product, which may contain up to 20% AVM B_1b.

Petitioner's Response to Deficiency 3c:

Since this is not stated as a true deficiency the Petitioner did not respond.

DEB's Response and Conclusions to Deficiency 3c:

In a discussion between F. Boyd (DEB), W. Dykstra (TOX I), and E. Budd (TOX I) on 6/15/89 it was (by TOX) concluded that a metabolism study of AVM B_1b is not necessary. Tox evaluation of technical AVM B_1 includes both B_1a and B_1b in all studies reported by the petitioner. Since the structural difference of the glycoside is only an addition of a methylene, it is expected that the predominant residue of B_1b would be the parent compound. Analytical methodology quantitates both B_1a and B_1b as AVM B_1 and its isomer.

It is concluded that Tox concurs with DEB and a metabolism study performed with AVM B_1b is unnecessary.

Deficiency 3d:

RCB defers to TB on the need for regulating the 24-hydroxymethyl AVM metabolite (free and conjugated). The 24-hydroxymethyl AVM metabolite accounts for 40 percent of the total radioactive residue (TRR) in kidney, 16.5 percent of the TRR in liver, 6 percent of the TRR in fat, and 11 percent of the TRR in milk.

Petitioner's Response to Deficiency 3d:

Based on Toxicology Branch reviews (12/31/87 letter), potential animal residues of 24-hydroxymethyl avermectin are not of toxicological concern and therefore do not require an analytical method.

DEB's Response and Conclusions to Deficiency 3d:

In a 6/6/89 meeting between members of Tox Branch I (E. Budd, W. Dykstra), DEB (V. F. Boyd, D. Edwards, R. Schmitt) and W. Burnam (HED), it was concluded that the 24-hydroxymethyl metabolite need not be specifically regulated at this time for the following reasons: (i) tolerance levels of 0.02 ppm for meat and meat by-products and 0.005 ppm for milk are sufficiently high to include any metabolite residues that may occur, and (ii) the toxicity of the metabolite is not expected to exceed that of the parent compound. The toxicologists did not conclude, however, that the 24-hydroxymethyl metabolite is not of toxicological concern. Rather, they concluded that if the tolerances for residues in meat and milk need to be raised at some future time due to registration of use on additional feed items, the 24-hydroxymethyl metabolite may need to be included in the tolerance expression and appropriate enforcement methods for its determination developed. Deficiency 3d is satisfied.

Deficiency 3e:

RCB concludes that the nature of the residue in ruminants is not adequately understood. The petitioner will need to conduct a goat metabolism study using ^{14}C-AVM; a higher dosage rate may be needed to identify the terminal residues.

Petitioner's Response to Deficiency 3e:

Merck maintains the nature of the residue in ruminants is adequately understood. Reference is made to the 9.5 page response presented on 1/21/88 in connection with the DEB review, 7/29/87, for cotton, PP#7F3500. The entire response was incorporated as Appendix 3 in F. Boyd's memo of 1/4/89 on PP#7F3500.

DEB's Response and Conclusion to Deficiency 3e:

In the above mentioned review memo of 1/4/89, we commented as follows:

> "For determining the degradation of a pesticide in animals or plants, DEB has never agreed to the use of H^3-labeling unless C^{14}-labeling is impossible. For the purpose of temporary tolerances, DEB accepted the H^3-labeled goat study when data were presented showing no exchange of the H^3-label.
>
> The goats were dosed with H^3-AVM at 0.005, 0.05, and 1.0 mg/goat/day for 10 days. The high level is at 20X the expected residue to be fed ruminants from citrus pulp. The specific activity of the H^3-labeled AVM was 1000X higher than the specific activity possible using C^{14} in the biosynthesis of the radiolabel. To use C^{14}-AVM with sufficient activity for identifying metabolites would require dosing the goat at 500X level based on citrus pulp residues.
>
> AVM was shown to be excreted by the goat as B_1a (parent), its 24-hydroxymethyl metabolite and 3"-desmethyl metabolite. A total of 99 percent of the radiolabeled dose was excreted in the feces with ca. 70 percent as B_1a, 20 percent as the 24-hydroxymethyl and 5 percent as 3"-desmethyl compound. No accumulation in tissues or milk was found.
>
> These data from the H^3-AVM goat studies are considered an adequate description of the nature of the residue in ruminants for assessing lower limit residues of AVM in feed (i.e., cottonseed) at a maximum of 25 percent with a tolerance of 5 ppb, which would contribute only 1.25 ppb AVM residues to the diet of beef cattle.
>
> DEB considers Deficiency 4c, as relates to cottonseed only, to be satisfied because of the low level of AVM expected in the diet of cattle. As the exposure of AVM becomes larger, the significance and necessity for a <u>proper</u> ^{14}C metabolism ruminant study becomes greater. The petitioner should be so informed."

As will be discussed in Deficiencies 5, 6 and 7 the residues in the citrus rac indicate that a tolerance proposal of 0.02 ppm would be appropriate, and consequently a proposed tolerance of 0.1 ppm would be appropriate for citrus oil and pulp, dried. The maximum exposure of cattle resulting from feeding cottonseed and citrus products would be a concentration of 0.035 ppm avermectin residues. This residue level is within the range used in setting dose concentrations in the goat metabolism study. The H^3-goat study is still considered sufficiently representative for

determining the fate of avermectin residues in the ruminant from a 0.035 ppm feed level. However, if, in the future, registration is proposed on additional feed items such that the dietary burden to livestock is increased, a new goat metabolism study with elevated feeding levels and use of a ^{14}C-label may be required.

The H^3 goat metabolism data is adequate for determining the fate of avermectin in the ruminant at the level of AVM residues expected in the diet of cattle. The residues of concern in animals fed citrus products bearing residues of abamectin are considered to be the parent compound and its 8,9-delta isomer. Deficiency 3e is considered satisfied.

Deficiency 4a:

At this time RCB cannot determine whether the methodology (Merck Method No. 1009R01) which was used to generate all citrus RAC data and determine AVM B_1a (and its delta-8,9 isomer) provided adequate residue data. Another Merck Method (No. 1009 Revision No. 2) recently (ACS/COB September 30, 1987) passed a successful EPA method validation. RCB will require bridging data between the two residue methodologies. To accomplish this bridging data, RCB recommends that selected RAC samples containing finite residues (i.e., > 5 ppb) be reanalyzed simultaneously by both

methods and the results reported and compared. Simultaneous reanalysis would alleviate any concerns RCB would have concerning storage stability of existing RAC samples.

As an example, RCB would suggest reanalysis of Sample Nos. 70402359, -60, -63, -64; 70403492, -93; 70402343, -44, -47, -48, -49, -50.

Petitioner's Response to Deficiency 4a:

Abamectin residue method #1009R02 was successfully validated by the EPA laboratory at Beltsville. The reviewer is concerned with the differences between #1009R01 which was used for the residue sample analyses and the validated method #1009R02. There are no laboratory differences between these two methods. Method #1009R01 was revised to correct several typographical errors, to clarify certain sections with more details, and a section added describing how to test and wash the aluminum oxide (if necessary). Both procedures would be used only rarely, for a bad lot. These procedures have not been used routinely by either Merck or any of the contract laboratories running these methods, and were added to the method at the request of the EPA.

Fortification recoveries and possible interferences are controlled with every analysis set by the requirement that each set of samples include both a control sample and a control sample spiked at the approximate level expected to be seen in the

samples in that analysis set (Merck Protocol AB-P1, Appendix 1). Possible problems seen in the control or fortified sample might suggest further testing of the aluminum oxide. In practice, we have had few problems which required such testing.

There is no need, and in reality, no way to bridge the two methods, as in the laboratory they are identical.

DEB's Response and Conclusions on Deficiency 4a:

DEB concludes that Methods 1009R01 and 1009R02 are, in practice, identical. We would recommend that a short preface to a method revision as to how, why and to what extent the method is being revised could prevent future misunderstandings.

Method #1009R02 is accepted as the enforcement method for monitoring abamectin residues in citrus. Deficiency 4a is considered satisfied.

Deficiency 4b:

At this time RCB cannot conclude that Merck Method No. 1004 Revision No. 1 is adequate to enforce the proposed food and animal feed additive tolerances. It seems that the petitioner needs to revise this method as per Method No. 1009 Revision No. 2, that is, to standardize the testing of aluminum oxide in the method. The petitioner must also adequately address RCB's questions regarding high background or baseline levels on orange and tangelo dried peel control and sample chromatograms and submit specific processed commodity (dried citrus peel and oil) recovery data reflecting any revisions (such as standardizing the aluminum oxide) made in the procedure.

Petitioner's Response to Deficiency 4b:

The addition of the testing and washing procedures for the aluminum oxide to Method #1004R01 does not change the method at all. It would still be run in the laboratory in exactly the same way; the testing/washing procedures are used only when there is a problem. For completeness and consistency, Method #1004R01 has been revised (1004R02) to include these procedures (Appendix 2).

The high baseline levels seen in some of the control chromatograms are artifacts of the chromatographic data system. The chromatogram full scale or "highest value" was defaulted to an inappropriately low level (such as 100 mv). In all cases where this occurred, the data were replotted to present the chromatograms with the appropriate scale. Both sets of processed data were given in the final report. Replotting did not affect the peak height or area counts (as shown on the examples in Appendix 3), but rather only modified the display of the

chromatogram. Two examples of such data taken from the citrus fractionation study are shown in Appendix 3.

Appendix 4 contains recovery data from the citrus fractionation study (001-86-035, -036, -037R) revised to show the sample matrix (orange, tangelo or grapefruit)which was used for each fortification sample. There were no modifications made of method #1004R01 for these sample analyses.

DEB's Response and Conclusions on Deficiency 4b:

The aluminum oxide testing and washing procedure is included as a revision to #1004R01 and is filed as a part of this amendment in #1004R02. The original method and revision are otherwise identical methods.

The orange and tangelo chromatograms in question were indeed presented twice - once full scale was reached on the computer it defaulted to an mv setting that defied graphic presentation of any peaks or background. The second presentation of such chromatograms (after reprocessing the data at an appropriate computer setting) allowed for a graphing of peaks and background which matched computer calculated concentrations of AVM. Computer calculations are the same as originally reported, only the graphic presentation was changed to a discernable chromatogram.

Recovery data are presented for the processed citrus commodities using either acetic anhydride or trifluoroacetic anhydride derivatization. Recoveries are better and more consistent with TFAA than with AA. However, at a level of 0.1 mg/ml in the prewash rinse the recoveries only averaged 61% for AVM even with TFAA. In all other fractions; whole fruit, dried peel, chopped peel, and oil - recoveries using TFAA averaged within the range of 74-101% for avermectin B_1a and 66-86% for delta 8,9-isomer. The methodology was that of #1004 Revision No. 2 and the same for all reported recoveries with exception of the derivatizing agent.

The 1009 No. 2 Method is accepted as the validated method for citrus (rac). The 1004 R02 Method is used for analysis of citrus pulp and oil. The latter method is essentially identical to 1009 No. 2, so it should not require validation.

DEB requests from the petitioner a copy of Method 1009 No. 2 incorporating that portion of Method 1004R02 necessary to accommodate analysis of the processed commodities of citrus. This method copy will be submitted to FDA for inclusion in PAM II as the enforcement method for citrus and its processed commodities.

The petitioner's reply to Deficiency 4b is considered adequate for satisfying the Deficiency, as stated, but a copy of the method as described, is required.

Deficiency 4c:

With regard to determining AVM residues in animal commodities, RCB cannot determine whether the proposed enforcement method (Merck Method No 32A) is adequate for enforcement purposes until this method has passed a successful EPA method validation. A favorable conclusion regarding the adequacy of the proposed animal commodity enforcement methodology is also contingent upon the results of the requested ^{14}C-AVM goat metabolism study and TB's opinion regarding the need to regulate the 24-hydroxymethyl AVM metabolite (free and conjugated). If additional residues are determined to be of toxicological concern (such as 24-hydroxymethyl AVM), then appropriate analytical methodology for determining that compound will be needed.

Petitioner's Response to Deficiency 4c:

The EPA has completed their validation of the abamectin method in tissues and milk; in informal conversation with the analysts at Beltsville, they found the methods to be satisfactory.

DEB's Response and Conclusion to Deficiency 4c:

In the memo of F. Boyd, PP#8F3592/FAP#8H5550, 9/2/88, Method No. 32A was validated as an adequate monitoring method for abamectin and its delta 8,9-isomer in meat and milk. Deficiency 4c is satisfied.

Deficiency 4d:

Ivermectin (22,23-dihydro AVM) is registered for use on large animals at a rate of 0.2 mg/kg body weight. The petitioner has said that the analytical methodology differentiates between ivermectin and AVM (C. Deyrup telecon with R. Dybas, Merck, July 2, 1987). RCB reiterates its need for chromatograms of representative animal commodities containing AVM and ivermectin to validate this claim.

Petitioner's Response to Deficiency 4d:

Previously discussed and accepted in pending petition for use of abamectin on cotton.

DEB's Response and Conclusions to Deficiency 4d:

In the F. Boyd memo of 1/4/89 data showing the ability to differentiate between ivermectin and avermectin were accepted. Deficiency 4d is considered satisfied.

Deficiency 4e:

Residue Chemistry Data Requirements in 40 CFR 158.125(b)(15) require that regulated pesticide residues be subjected to one or more of the multiresidue procedures published in an Addendum to Pesticide Assessment Guidelines Subdivision O - Residue Chemistry Data Requirements for Analytical Methods in 40 CFR 158.125, Multiresidue Protocols.

Petitioner's Response to Deficiency 4e:

A Hazleton Lab report on a multiresidue study involving the LC Method is contained in Appendix 5.

DEB's Response and Conclusions to Deficiency 4e:

The entire Appendix 5 report has been forwarded to FDA for evaluation. The deficiency is considered satisfied.

Deficiency 5a:

In the absence of the yet to be submitted storage stability data for both AVM B_1a and its delta-8,9 isomer on orange, lemon, and grapefruit, RCB cannot arrive at a final conclusion regarding the integrity of submitted citrus RAC samples.

Petitioner's Response to deficiency 5a:

Additional stability data for abamectin and the delta 8,9-isomer are given in Appendix 6. Citrus samples (oranges, lemons and grapefruit) were spiked at approximately 10 and 50 ng/g avermectin B_1a and at 10 ng/g B_1a delta 8,9-isomer, and stored in a freezer. Samples have been assayed at 0, 1, 3 and 6 months; with each analysis set a control and a fresh fortification is run as a check on the method. Data through 6 months show no loss upon storage of either abamectin or the delta 8,9-isomer.

DEB's Response and Conclusions to Deficiency 5a:

The storage stability determinations were made at 0, 1, 3, 6 and 12 months for AVM B_1a, B_1b and the 8,9-isomer. Data are presented for oranges, lemons, and grapefruit. Recoveries in the spiked, stored samples demonstrate no detectable loss of any of the three chemical entities during 12 months of freezer storage.

Storage stability data support the integrity of the previously submitted residue data and Deficiency 5a is considered to be satisfied.

Deficiency 5b:

At this time, RCB can draw no conclusions on the adequacy of the residue data until the petitioner submits the requested bridging or validation data for Method No. 1009 Revision No. 2 and offers adequate documentation and justification as to why the residue values on oranges obtained from the two California locations (Santa Paula and Tulare counties) should not be considered. In addition, if TB expresses concern regarding unidentified polar degradates of AVM which may comprise up to 70 percent of the total terminal residue in citrus, then the petitioner must revise the tolerance expression to include identified polar degradates, develop validated enforcement analytical methodology to determine these degradates, and generate additional citrus residue data utilizing this methodology.

Petitioner's Response to Deficiency 5b:

Response to the request for bridging or validation data is the same as given in 4b. Citrus residue trials 001-86-196R and 001-86-596R are considered as supplemental data. The above studies were previously submitted as supplemental. The information in Appendix 7 is being submitted to further support the invalidity of results of these trails.

DEB's Response and Conclusions to Deficiency 5b:

DEB agrees that the bridging data question is adequately handled in 4b. Citrus trials 001-86-196R and 001-86-596R, however, cannot be considered as supplemental data:

(1) If three trials are reported in CA with adequate matching control sample data at < 0.002 ppm residues in each trial, then the two trials reporting finite residue have more validity than the single trial reporting no residue in treated fruit.

(2) For protection of the grower, who will use the label, it is important that the petitioner present data obtained from the use of the product through commercial application. We find no real valid explanation of why the difficulty in calibrating equipment for determining dosage to small plots should negate the field results. It may be more representative of actual agricultural practice.

(3) The petitioner has had time to rerun these trials if the results were invalid. Since residue levels many times vary greatly from FL to CA, it is necessary that more than one residue trial be used for determining residue levels in CA citrus.

These two CA trials from Santa Paula and Tulare counties cannot be considered supplemental data. The finite residue levels will need to be used in setting a tolerance in the absence of no further CA trial data (other than a single trial showing no finite residue).

In summary, the residue data show levels of avermectin B_1 and its delta 8,9-isomer in citrus as:

oranges	- < 0.002 - 0.011 ppm
grapefruit	- < 0.002 ppm
tangelos	- < 0.002 ppm
lemons	- < 0.002 ppm

Since the finite residues in CA oranges are reported as 0.008 and 0.011 ppm, then a proposed tolerance of 0.005 ppm would be inadequate for the proposed use. A tolerance level of 0.02 ppm for the rac citrus would appear appropriate.

Deficiency 5b is not considered satisfied.

Deficiency 6b:

RCB, at this time, is unable to comment on the adequacy of the proposed food/feed additive tolerance in citrus oil and pulp until RCB's remaining questions regarding the nature of the residue in plants, adequacy of the submitted residue data, validation of Merck Method No. 1004 Revision 1 and submission of relevant sample storage stability data by the petitioner have all been addressed.

Petitioner's Response to Deficiency 6b:

These issues have been addressed elsewhere.

DEB's Response and Conclusions to Deficiency 6b:

The processing study data show a concentration factor of 5X from citrus rac to dried peel and oil. When this factor is applied to a proposed tolerance of 0.02 ppm, then an adequate tolerance for dried citrus pulp and citrus oil would be 0.10 ppm.

An increased proposed tolerance will be necessary for dried pulp. Deficiency 6b is not satisfied.

Deficiency 7a:

The residue data from the cattle feeding study did not include analyses for the 24-hydroxymethyl metabolite or its conjugate. This metabolite has been found to comprise 40 percent of the TRR in goat kidney. If TB should conclude that 24-hydroxymethyl AVM and its conjugate are of toxicological concern, feeding studies reflecting analyses for these metabolites will also be required.

Petitioner's Response to Deficiency 7a:

The issue of the 24-hydroxymethyl metabolite has been previously addressed.

DEB's Response and Conclusions to Deficiency 7a:

The increased tolerances referred to in 5b and 6b when related to animal feed could result in quantities of 24-hydroxymethyl metabolites in liver as high as 7 ppb (0.007 ppm) and in milk as high as 0.8 ppb (< 0.001 ppm). Method sensitivity for 24-hydroxymethyl metabolite would be expected to be no better than 0.002 ppm.

The Toxicology Branch (I) has concluded that the 24-hydroxymethyl metabolite does not need to be specifically regulated in meat or milk in connection with use on citrus (refer to DEB response re. deficiency 3d). Thus, deficiency 7a is satisfied.

Deficiency 7b:

RCB at this time, is unable to comment on the adequacy of the proposed permanent tolerances on cattle meat, meat by-products, and milk until the nature of the residue in ruminants is adequately understood, the proposed enforcement methodology for animal commodities has passed a successful EPA method validation and the need to include 24-hydroxymethyl AVM in the tolerance expression for animal commodities has been determined.

Petitioner's Response to Deficiency 7b:

These issues have been addressed elsewhere.

DEB's Response and Conclusions to Deficiency 7b:

The residues to be regulated in meat and milk are AVM B_1 and its delta 8,9-isomer (refer to DEB response to Deficiency 3d), which are adequately determined by the validated method of analysis (discussed above in Deficiency 4c). However, the proposed tolerances for meat and meat by-products (0.005 ppm) and milk (0.001 ppm) are considered inadequate due to the necessity for increased tolerances for citrus rac and feed items.

Using a hypothetical diet for beef and dairy cattle based on a maximum use of cotton and citrus feed items, we find:

Ingredients	% in Diet Beef	% in Diet Dairy	AVM Residues in ppm (found in ingredients)	Maximum (ppm) AVM Residues Fed Beef	Maximum (ppm) AVM Residues Fed Dairy
Cottonseeds	25	20	0.005		
meal	15	15	0.005		
hulls	15	5	0.005	0.003	0.002
Citrus pulp	33	33	0.100	0.033	0.033
Corn	12	27	-	-	-
Total				0.036	0.035

Using the feed factor (dose) for dairy cattle at 0.035 ppm, we can estimate the potential maximum residues of AVM B_1 in meat and milk. The 28-day feeding study (submitted with PP#7G3468) was performed in dairy cattle at levels of 10 ppb, 30 ppb or 100 ppb of AVM residues in the diet. The following levels of AVM were detected:

Dose (ppb)	AVM Level (ppb) Liver	Muscle	Fat	Kidney
10	3-4	1-2	2	1-2
30	5.0-7.6	2	4-6.0	2
100	18-20	2	9.8-14	4-5

Therefore, from feeding 35 ppb of residues we might anticipate a maximum of approximately 9 ppb residues in meat or meat by-products. During the feeding study there were no residues in milk from the 10 ppb feeding and only one sample during the 28 days of feeding 30 ppb contained a 1 ppb residue. At the highest feeding of 100 ppb the maximum residue in milk was 4 ppb at Day 14, with only 1 ppb found at Day 28. We would therefore expect 2 ppb or less residues in milk from feeding 35 ppb.

The proposed tolerances are inadequate for meat and milk. A new Section F proposing tolerances of:

cattle - meat and meat by-products - 0.02 ppm
- milk - 0.05 ppm

would seem appropriate. Deficiency 7b is not considered satisfied.

cc: EAB, Circu., R.F., PP#8F3592/FAP#8H5550, Reviewer (F. Boyd), PMSD/ISB (Eldredge), R. Tomerlin (MS/SACB)
RDI:D.F.Edwards:6/19/89:R.Loranger:6/19/89:
H7509C:DEB:F.Boyd:CM#2:Rm810:557-7484:Typist(mb):6/15/89