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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#6F3362/FAP#6H5493 - Metalaxyl and Mancozeb on Grapes (DEB Nos. 5557 and 5558) Evaluation of Amendment Dated June 23, 1989 (MRID No. 411501-01)

FROM: Gary F. Otakie, P.E., Chemist
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and

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THRU: Richard D. Schmitt, Ph.D., Chief
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Edward Zager, Jr.

Ciba-Geigy has submitted this amendment consisting of a cover letter from Karen S. Stumpf, Senior Regulatory Specialist to Susan Lewis, Acting PM 21, RD/EPA; revised Sections B and F and MRID No. 411501-01 containing data on residues of metalaxyl, ethylene bisdithiocarbamate (EBDC), and ethylene thiourea (ETU) on grapes, pomace, raisins, raisin waste, juice, yeast and wine.

This amendment is in response to the EPA request of S.T. Lewis "Mancozeb Over Tolerance Residues Reported Under Section 6(a)(2)" March 23, 1989 for the Special Review on mancozeb and to a DEB memorandum (see October 14, 1988 memorandum of S. Hummel) noting overtolerance residues of mancozeb from the use pattern proposed in PP#6F3362/ FAP#6H5493 and requesting either the proposed use pattern for Ridomil MZ58 be altered, or higher tolerances be proposed for mancozeb in grapes; and further that Ciba-Geigy submit the residue data collected including analyses for mancozeb, ETU, and metalaxyl and that the residue data be reviewed for the EBDC Special Review.

This amendment is also in response to DEB's original review of PP#6F3362/FAP#6H5493 (see March 20, 1986 memorandum of M. Firestone) which indicated that Deficiencies 1a, 1b, 4b, 5, 6, 7, and 8 remain unresolved.

Conclusions:

1. A copy of the proposed label must be provided to assure DEB that application directions and use restrictions are sufficiently specific and clear.

2. The petitioner's proposal to establish a 1 ppm tolerance with regional registration for residues of metalaxyl on grapes is not acceptable. No justification for such a tolerance has been provided according to 51 FR 63 (April 2, 1986). Residues of metalaxyl in the raw agricultural commodity (RAC) grapes from one California field trial (AG-A No. 10080) exceeded 1 ppm (1.4 ppm) following the proposed use. Furthermore, this sample was stored for 20 months prior to analysis and therefore since no storage stability data are available to support such an interval, residues may have been even higher at harvest. The petitioner must either submit a revised Section F with a tolerance proposal of 2 ppm for grapes or provide an acceptable rationale as to why the 1.4 ppm California value may be considered an outlier.

3. The petitioner's method of calculating maximum concentration factors for residues of metalaxyl in process fractions results in unrealistically high values. The petitioner compared the lower residue value for two individual grape samples with the residue value in the process fraction derived from a composite of the two samples. A more realistic approach is to compare the average value for the two raw grape samples with the process fraction value, assuming the petitioner

can certify that the composite samples represented a mixture of equal weights of the individual samples. This results in maximum concentration factors of < 5X for pomace and raisin waste and 3X for raisins, as opposed to the petitioner's calculations of < 4X for raisins and < 7X for raisin waste. Thus, if a 2 ppm tolerance is proposed for grapes (see above), the revised Section F should also include proposed tolerances of 10 ppm for pomace (wet and dry) and raisin waste, and 6 ppm for raisins. Alternatively, if the petitioner is able to adequately provide a rationale for maintaining the RAC tolerance at 1 ppm, the revised food/feed additive tolerances should be 5 ppm for pomace (wet and dry) and raisin waste, and 3 ppm for raisins.

4. The nature of the residue in animals is not adequately understood and new metabolism studies are required (refer to September 1988 Guidance Document for Metalaxyl).

5. A determination concerning proposed analytical methodology for determining residues of metalaxyl in animal commodities is reserved pending submission of acceptable animal metabolism studies with radiolabeled validation of the enforcement analytical methodology.

6. The likelihood of secondary residues of metalaxyl in meat, fat, milk, poultry and eggs resulting from ingestion of the feed commodities, pomace and raisin waste, and the need for new feeding studies cannot be deter- mined until acceptable animal metabolism studies are available.

7. Metalaxyl metabolite CGA-94689 must be subjected to FDA Multiresidue Protocols A-E as described in the recent revision (April 1989) of Appendix II of the Pesticide Analytical Manual, Vol. I.

Recommendation

At this time DEB recommends against the proposed metalaxyl tolerances for the RAC grapes and its processed fractions for the reasons cited above under Conclusions 1-6.

Also, since mancozeb is an EBDC currently in Special Review and the data reflecting processing of samples collected in Trial #AGA-10080 may provide useful information for dietary exposure assessment, additional information regarding the conduct of this study are required as follows:

- Detailed information pertaining to the methods used in processing grapes to juice and wine must be provided. For example, information regarding pasteurization of juice, and fermentation and aging temperatures and times for wine must be provided.

- Detailed information regarding storage times and conditions from harvest to analysis for both raw and processed samples from AGA-10080 must be provided. This information must include time and temperatures maintained during transport from the field to Ciba-Geigy facilities and from Ciba to the EBT labs. Also, the time and conditions of storage of extracts between extraction and analysis, thawing time of samples prior to analysis, and the exact date of processing must be provided. A summary of the required information along with all pertinent raw data sheets must be submitted.

Note for EBDC Special Review

The grape EBDC and ETU residue and processing data in this submission are not valid since the samples were stored up to 20 months before analysis and storage stability data run concurrently at the same laboratory were not provided. However, since they may provide useful information to be considered in the EBDC Special Review, a discussion of the data is provided.

The EBDC application rates utilized were 0.3X to 0.9X the 3.23 lb ai/A established single application rate with a preharvest interval (PHI) from 38 to 76 days compared with the established PHI of 66 days in all States except California, where mancozeb is not applied after fruit set (built-in PHI of 80-90 days). Nevertheless, two field trials conducted in California with 66-day PHIs at an application rate of 0.5X to 0.9X (AG-A Nos. 9994 and 10080) resulted in EBDC residues as high as 8.0 and 19 ppm, respectively. Because of possible significant EBDC degradation from sample storage up to 20 months before analysis (i.e., the actual EBDC residues were in all probability considerably higher than the EBDC reported residue levels), even considering that the PHI for mancozeb in California, where the field trials were conducted, is not to apply after fruit set which can range from 80 to 120 days, the data do indicate a possibility of overtolerance residues (tolerance = 7 ppm) from the established use of mancozeb on grapes in California and other States in the western region, especially in light of the current label's lack of a maximum seasonal application rate.

Concerning the wine processing data in this submission and in light of other wine processing data on mancozeb submitted by Rohm & Haas, it appears that a significant portion of the EBDC residue in grapes is degrading to ETU during the winemaking process. Data in this submission indicate ETU residues in wine as high as 13 percent of the EBDC residue in grapes (i.e., 19 ppm EBDC in grapes, and 2.5 ppm ETU and no detectable EBDC in wine). Data on the winemaking processing studies are inadequate to make a determination as to whether they are representative of current wine production technology in the United States. Data on fermentation times and temperatures, both parameters which could affect ETU formation, were not provided. The stability of ETU and/or EBDC during the wine storage/aging process is also unknown. Wine processing studies utilizing ripe grapes and reflecting current technology are unavailable (according to Prof. Roger Bolton of the University of California, fermentation temperature and time for red wine should be 80 to 90 °F for 1 week and for white wine 55 to 65 °F for 3 weeks with fermentation occurring in a controlled hot water bath with 1 percent solids and a pH of 3.5, followed by 6 months aging at 60 °F and 45 °F for red and white wine, respectively).

Since such data are not currently available it may be advisable to utilize the worst case from all the available, wine processing data to estimate ETU residues in wine (i.e., EBDC conversion) as a percentage of EBDC grape residues and include this estimate in the Dietary Exposure Analysis for mancozeb and ETU. Utilizing the wine processing data in this submission and the revised Dietary Exposure Analysis for mancozeb and ETU (see August 17, 1989 memorandum of S. Hummel) which assumed a mancozeb residue in unwashed grapes of 0.83 ppm, would result in an estimated ETU concentration in wine (0.83 ppm x 13%) of 0.108 ppm.

The wine processing data do support the hypothesis that the conversion of EBDCs to ETU may be a temperature-sensitive reaction for processed grape products. Accordingly, currently available processing data on ETU residue levels in grape juice may not be indicative of actual ETU residue levels in grape juice if these studies did not reflect commercial hot pressing (i.e., juice temperatures ranging from 140 to 145 °F) and commercial pasteurization (i.e., juice temperatures ranging from 175 to 180 °F per Fruit and Vegetable Juice Processing Technology by Donald K. Tressler and Maynard A. Joslyn, 1961).

Present Submission

1. Revised Tolerance Proposals

Section F

Proposed Pesticide Tolerances

A tolerance for combined residues of the fungicide, metalaxyl [N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester], and its metabolites containing the 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl) alanine methyl ester, each expressed as metalaxyl, in or on the raw agricultural commodity grapes at 1.0 part per million (ppm).

Proposed Food/Feed Additive Tolerances

Food/feed additive tolerances for combined residues of the fungicide, metalaxyl [N-(2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester] and its metabolites containing the 2,6-dimethylaniline moiety, and N-(2-hydroxy-methyl-6-methylphenyl)-N-(methoxyacetyl) alanine methyl ester, each expressed as metalaxyl, in or on the following processed foods:

Wet and Dry Grape Pomace	at 5.0 ppm
Raisins	at 4.0 ppm
Raisin Waste	at 7.0 ppm

2. Revised Section B

Grapes (Eastern and Midwestern Only)

"Apply 0.87-1.16 lb ai of Ridomil MZ58/A (0.15-0.2 lb ai of metalaxyl + 0.72-0.96 lb ai of mancozeb) in sufficient water to provide thorough coverage. Begin applications early in the season (shoot growth 1 inch) when conditions are favorable for downy mildew and make three applications at 14-day intervals.

"For control of bunch rot and dead arm plus heavy downy mildew, make three applications at 14-day intervals as follows:

"1st Application - 1.45 lb ai of Ridomil MZ58/A (0.25 lb ai of metalaxyl + 1.2 lb ai of mancozeb).

"2nd Application - 1.45 lb ai of Ridomil MZ58/A (0.25 lb ai of metalaxyl + 1.2 lb ai of mancozeb).

"3rd Application - 1.74 lb ai of Ridomil MZ58/A (0.30 lb ai of metalaxyl + 1.44 lb ai of mancozeb).

"Notes: To avoid possible illegal residues, (1) do not apply within 66 days of harvest and (2) do not apply more than 4.64 lb ai of Ridomil MZ58/A per season (0.8 lb ai of metalaxyl + 3.84 lb ai of mancozeb)."

3. Additional Data

The present submission also includes additional metalaxyl, mancozeb, and ETU residue data for grape field trials (including processed grape fractions from New York and California) conducted in New York, California, Minnesota, Arkansas, and South Carolina in 1983, 1986, and 1988, a discussion of the basis for the proposed tolerances in the RAC and the processed grape fractions, and a discussion of the maximum level of secondary residues expected in animal commodities resulting from established metalaxyl uses and from the proposed use on grapes.

Detailed Considerations

The deficiencies listed in DEB's March 20, 1986 review (i.e., Nos. 1a, 1b, 4b, 5, 6, 7, and 8) and the deficiencies listed in DEB's October 14, 1988 review (i.e., Nos. 1 and 2) are outlined below followed by the Petitioner's Responses and DEB's Comments/Conclusions.

Deficiency No. 1a (March 20, 1986)

The proposed label should be revised to clearly state the recommended application rate of the formulation Ridomil MZ58 (i.e., 1.5 to 2.0 lb of the formulated product per acre . . .).

Deficiency No. 1b (March 20, 1986)

A restriction as to the maximum number of applications or total amount of product applied per growing season should be included in a revised Section B/proposed label. This restriction should be supported by available residue data (Note: the available residue data reflect five applications).

Deficiency No. 1 (October 14, 1988)

Based on the reported overtolerance residues of mancozeb from the use pattern proposed in PP#6F3362/ FAP#6H5493, either the proposed use pattern for Ridomil MZ58 must be altered, or higher tolerances must be proposed for mancozeb in grapes.

Petitioner's Response to Deficiency Nos. 1a, 1b, and 1

The petitioner has submitted a revised Section B with a 66-day PHI and three applications at 14-day intervals totaling a maximum of 4.64 lb ai of Ridomil MZ58 with use limited to eastern and midwestern States. Although the revised Section B expresses the application rate in terms of lb ai/acre, the Master Introduction and Summary of the current submission states that the revised label expresses the application rate in pounds of formulated product, as follows:

> Directions for Use (Revised Label) For Eastern and Midwestern Grapes Only:
>
> Apply 1.5-2.0 lb of Ridomil MZ58 Product per acre in sufficient water to provide thorough coverage. Start applications early in the season (shoot growth 1 inch) when conditions are favorable for downy mildew, and make three applications at 14-day intervals. In order to control higher downy mildew pressure plus bunch rot and dead-arm; make three applications as follows: 2.5 lb then 2.5 lb then 3.0 lb of Ridomil MZ58 Product per acre at the recommended 14-day interval.
>
> Notes: A maximum of 8 lb of Ridomil MZ58 product may be used per season with a 66-day preharvest interval. For late season disease control apply other approved fungicides.

The petitioner also submitted a letter dated June 23, 1989 which states:

> "1. Five copies of proposed labeling which incorporate a new use pattern for grapes and preharvest interval of 66 days. In the RCB review of March 20, 1986, the reviewer stated that the label should make clear that the rates recommended are for the formulated product. Ciba-Geigy believes the label as written is clear. Directions for use for the crops already on the registered label are expressed in terms of pounds of Ridomil MZ58 per acre.

Because Ridomil MZ58 is the name of the formulated product, there should be no question as to what is intended.

"2. Three copies of a revised Section B which give the maximum amount of product that can be applied per season. The revised label also includes this restriction. The preharvest interval has been revised from 7 to 66 days to coincide with the residue package. Application has been restricted to Eastern and Midwestern grapes only. This use will not be registered in California."

DEB Comments/Conclusions Re: Deficiency Nos. 1a, 1b, and 1

The revised Section B clearly states the recommended application rate of the formulated product (i.e., Ridomil MZ58) in terms of ai/acre and specifies for severe conditions three applications of Ridomil MZ58 (i.e., 1.45, and 1.74 lb ai/A) at 14-day intervals, and prohibits the use of more than 4.64 lb ai of the formulated product per season (0.8 lb ai of metalaxyl and 3.84 lb ai of mancozeb).

Although the current submission does not include a copy of the revised label, the Master Introduction and Summary of the petitioner's response states that the revised label application rates are in terms of pounds of formulated product per acre. Nevertheless, a copy of the revised label is required and should be included in future submissions.

The petitioner has apparently proposed a label with regional use for a major crop to negate the overtolerance (proposed) residues detected in the California field trial, AG-A No. 10080 (1.4 ppm metalaxyl). The petitioner has not followed the Policy Statement on Minor Uses of Pesticides published in the FEDERAL REGISTER Vol. 51, No. 63, Wednesday, April 2, 1986 and no justification for approval of a tolerance with regional registration has been made. Further, it appears that proposed regional use on grapes would not meet the criteria set forth in the FR Notice since there is a likelihood of use of the pesticide outside of the proposed geographically limited area and the proposed use results in finite residues that are highly variable. Accordingly, either higher tolerances must be proposed for metalaxyl on grapes to account for the residues detected in the California field trial or a rationale must be provided as to why this value may be considered an outlier.

Deficiency Nos. 1a and 1b (March 20, 1986) remain unresolved. The petitioner also needs to submit a copy of the proposed label showing the application rate of the

formulated product and a restriction as to the permissible amount of product to be applied/growing season.

Deficiency No. 4b (March 20, 1986)

Present submissions of mancozeb residue data need to be accompanied by residue data for the EBDC metabolite ethylene thiourea (ETU). In the future, if there are any additional residues of concern identified during the Special Review process, residue data for these compounds will need to accompany submissions of mancozeb (EBDC) residue data; appropriate methodology would also be needed.

Deficiency No. 5 (March 20, 1986)

No new residue data have been submitted with this petition; rather, data first submitted with PP#4G3031/ FAP#4H5425 have been resubmitted (see L. Cheng memorandum of May 30, 1984, for a previous review). In the above review, the petitioner was advised that for a permanent tolerance petition, additional residue data should be submitted. Although the available metalaxyl residue data values do not exceed the proposed 2.0 ppm tolerance, RCB concludes that additional field trials should be conducted in the States of California and New York (i.e., single field trials in these major grape-growing States are not adequate).

Deficiency No. 6 (March 20, 1986)

The maximum proposed Ridomil MZ58 application rate would allow a treatment of 0.96 lb mancozeb/A, considerably less than the registered maximum use rate of 3.2 lb ai/A on grapes. At the minimum proposed preharvest interval (PHI) of 7 days, mancozeb residues in/on grapes ranged from 0.71 to 5.9 ppm and 1.5 to 12.0 ppm as a result of treatment at the 1X rate and the 2X rate, respectively. Mancozeb residue levels resulting from treatment at the 1X rate did not exceed the established 7 ppm tolerance for grapes (see 40 CFR 180.176); however, additional mancozeb and ETU data should be generated in the California and New York residue field trials requested above. The petitioner's reserve samples will also need to be reanalyzed for ETU residues provided that proper storage conditions would ensure valid ETU residue data. Otherwise, ETU residue data would need to be generated on new samples.

Deficiency No. 2 (October 14, 1988)

Ciba-Geigy should submit the residue data collected, including analyses for mancozeb, ETU, and metalaxyl. The residue data should be reviewed for the EBDC Special Review

even if Ciba-Geigy is not resolving the balance of the deficiencies in PP#6F3362/FAP#6H5493.

Petitioner's Response to Deficiency Nos. 4b, 5, 6, and 2

Summary tables of the residue results and processing studies are included as Attachment 1 to this review as Tables II thru V (Note: the tables are numbered as submitted).

The petitioner's response is as follows:

Results

"Grape samples collected in field tests using the proposed maximum 1X-rate treatment regime of 2.5 + 2.5 + 3.0 lb/A of formulated product (Ridomil MZ58) with a 14-day application interval and 66-day preharvest interval (PHI range 38-76 days) were analyzed for total metalaxyl and mancozeb residues. Residue data are presented in Table II. A total of seven field trials (Eastern and Midwestern States) were conducted in New York, Michigan, Arkansas, and South Carolina. Three of the seven trials included plots receiving a 2X treatment of 5.0 + 5.0 + 6.0 lb/A of formulated product (Ridomil MZ58) for residue comparison purposes. Grape samples receiving the proposed maximum 1X rate (2.5 + 2.5 + 3 lb/A formulated product) and harvested at 66 days following the last application contained a maximum total metalaxyl residue of 0.50 ppm (reported as metalaxyl equivalents) and a maximum total mancozeb residue of 4.24 ppm (4.2 ppm as EBDC and 0.04 ppm as ETU). Total metalaxyl residues in grapes resulting from the proposed treatment regime support the proposed 1.0 ppm tolerance for metalaxyl and mancozeb residues are also below the established 7.0 ppm tolerance for mancozeb.

"Although the application of Ridomil MZ58 to Western grapes is not a requested use, residue data from three studies conducted in California using the same treatment regime proposed for Eastern and Midwestern grapes are presented as supporting data (Table III).

Field Procedures

"Mature grape samples were collected at preharvest intervals ranging from 7 to 76 days following the final application of Ridomil MZ58. Residue samples were collected according to Ciba-Geigy SOP No. 7.10 (SOP in place for 1986 and 1988 field trials). Samples were collected at random from within the plots, taking care not to sample near the edges or to allow cross-contamination from different plots. The samples were not trimmed, cleaned, or washed.

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"After collection, samples were frozen and shipped with dry ice to Ciba-Geigy Corporation, Greensboro, North Carolina. Upon arrival, samples were stored frozen at -20.6 `C to -17.8 `C until they were prepared for analysis. Grape samples (AG-A 10080) were processed into fractions by Ciba-Geigy personnel at the Ciba-Geigy Research Farm, Fresno County, California immediately following harvest. Sample preparation was performed according to the FDA Pesticide Analytical Manual, Vol. I, Section 141 and Ciba-Geigy SOP No. 7.2 (SOP in place for 1986 and 1988 field trials). After preparation, the samples were stored in polyethylene bags labeled with field test number, AG-A number, sample code number, project number, and crop identification and returned to the freezer until analyzed by Ciba-Geigy or shipped to Enviro-Bio-Tech.

"All subsamples were weighed within eight hours after removal from the freezer and then extracted and analyzed for metalaxyl residues in the Ciba-Geigy Laboratories (Greensboro, North Carolina), or in the Enviro-Bio-Tech Laboratories (Bernsville, Pennsylvania)."

Analytical Procedures

"Residues of metalaxyl and its metabolites containing the 2,6-dimethylaniline moiety ('total' residues) were determined by Analytical Method AG-395. The validation of method AG-395 is reported in ABR-83033. Crop samples are extracted by refluxing with 80% (v/v) methanol/water for two hours. A 2-g aliquot of the sample is evaporated to dryness. One or one and a half ml of water is added to dissolve the residue, depending on the substrate, and the sample is refluxed for 15 minutes after addition of 10 ml of methanesulfonic acid (reflux time was reduced to 10 minutes for 1988 and 1989 analytical work). The extract is basified after the addition of water. The 2,6-dimethylaniline formed in the reaction is steam distilled.

"The steam distillate is cleaned up with silica SepPak cartridge. Trifluoracetic acid is added to the eluate to form a salt with 2,6-dimethylaniline (DMA-TFA) and the sample concentrated prior to analysis by capillary gas chromatography using a nitrogen/phosphorus detector operating in the nitrogen-specific mode. The trifluoroacetic acid addition step (Section 5.7.6) for the formation of DMA-TFA was found to be unnecessary and was omitted from the analytical procedure for 1988 and 1989 analytical work. For this latter work 2,6-dimethylaniline standard solutions were used for quantification.

"The analysis of mancozeb (EBDC) is performed according to Enviro-Bio-Tech SOP EBT-201.00 'Standard Operating

Procedure for Determination of Dithiocarbamate Residues by the Carbon Disulfide Evolution Method'. The analysis is based on refluxing the sample with boiling dilute acid. Evolved CS_2 is carried by gas stream through a trap to remove H_2S and other volatile interferences. It then reacts in a second trap with a color reagent to form a yellow complex, the cupric salt of N,N-bis(2-hydroxyethyl) dithiocarbamic acid, which is measured colorimetrically at 435 nm. The standard curve is constructed by carrying various amounts of analytical standards through the procedure. All of the standard results are then utilized to construct a standard curve using linear regression.

"The analysis of ETU is performed according to Enviro-Bio-Tech SOP EBT-200.01 'Standard Operating Procedure for Determination of Ethylene Thiourea in Crops and Feed'. ETU is extracted from the crop sample by homogenization in methanol. The extract is concentrated by rotoevaporation and added to a chromatographic column containing aluminum oxide. The column is then eluted with methanol. The resulting sample extract is derivatized with chloroform, exchanged into toluene and analyzed by gas chromatography with a flame photometric detector (sulfur mode). External standards of various concentrations of butyl-ETU in toluene are analyzed with the samples. Measured peak heights are used to construct a standard curve over the range of interest. By using the appropriate dilution factor for sample size injected, results of each analysis are reported on a ppm (ug/g) basis."

Method Recovery Validation Data

Procedural recovery of total metalaxyl residues from fortified control samples of grapes and grape fractions using Analytical Method AG-395 ranged from 0.05 to 15 ppm of metalaxyl. Recoveries averaged 88.4% $\pm$ 17.7% (n=44).

"Fortification levels of EBDC ranged from 0.10 to 24 ppm. Recoveries averaged 94.0% $\pm$ 2.7% (n=28). Fortification levels of ETU ranged from 0.01 to 0.50 ppm. Recoveries averaged 89.7% $\pm$ 9.9% (n=19)."

Storage Stability

"Freezer storage stability data, ABR-80028 and ABR-86044, were previously reported. Metalaxyl residues were shown to be stable for at least eighteen months when stored under freezer storage conditions (-15 `C). All samples presented in this report, including the commercial processing samples, were stored between one and twenty months prior to analysis. One study out of 14 was analyzed after twenty months of freezer storage, two months longer than the

eighteen-month storage data. Although, metalaxyl storage data are available only for eighteen months, degradation of residues determined as 2,6-di-methylaniline beyond eighteen months is unlikely. The data reported herein are therefore valid and not affected by freezer storage."

Residue Results

"Residue results for grapes from Eastern or Midwestern States using the proposed three foliar applications of Ridomil MZ58 at 1.45 lb/ai plus 1.45 lb/ai plus 1.74 lb ai/A (or 2.5 + 2.5 + 3.0 lb/A of formulated product) are presented in Table II. Supporting residue data from grapes grown in California are presented in Table III. Further field test and sample specific details can be found in the individual analytical (AG-A) reports. The proposed use directions imposes a preharvest intervals (PHI) of 66 days. Results in Table II also include grape samples harvested at 38-day and at 72-76 day PHIs. The maximum 1X metalaxyl residue value in or on grapes harvested at a 66-day PHI was 0.50 ppm. Maximum 1X mancozeb residues were 4.2 ppm as EBDC (72-day PHI) and 0.04 ppm as ETU, or 4.24 ppm as combined mancozeb residues, which is within the established tolerance of 7 ppm of mancozeb in or on grapes."

DEB Comments/Conclusions Re: Deficiency Nos. 4b, 6, and 2

The petitioner conducted additional field trials in California and New York analyzing samples for residues of metalaxyl, EBDC and ETU as was requested in DEB's March 20, 1986 review.

The residue data from the new field trials (reference Attachment 1) were below the proposed tolerance for metalaxyl on grapes in all States except California. Residue levels for EBDC and metalaxyl in grapes for the field trials in New York, Michigan, Arkansas, and South Carolina were below the proposed metalaxyl tolerance of 1.0 ppm and the established EBDC tolerance of 7.0 ppm (PHIs from 38 to 76 days); with metalaxyl residues ranging from < 0.05 to 0.50 at a 1X application rate (i.e., 2 x 1.45 + 1.74 lb ai/A) and from < 0.05 to 1.08 ppm at a 2X application rate (i.e., 2 x 2.90 + 3.45 lb ai/A); EBDC residues ranging from 0.15 to 4.2 ppm at a 1X application range and from 0.18 to 5.7 ppm at a 2X application rate; and ETU residues in grapes ranged from < 0.02 to 0.04 ppm for both the 1X and 2X application rates. However, the residue data from the field trials in California indicate metalaxyl residue levels above the proposed 1.0 ppm tolerance and EBDC residue levels above the established 7.0 ppm EBDC tolerance level following treatment according to the proposed use in other States. The highest residues were from AGA No. 10080 where samples were stored 20 months before

analysis and a 1X application rate resulted in metalaxyl and EBDC residues of 1.4 and 9.3 ppm, respectively. ETU residue in grapes from the California field trials ranged from < 0.02 to 0.27 ppm for both 1X and 2X application rates.

The analytical methods and fortification levels used and the method recoveries obtained for metalaxyl, EBDC, and ETU of 60 to 130 percent, 90 to 98 percent, and 76 to 105 percent, respectively, appear acceptable. The grape fruit samples were stored frozen at -15 °C from 1 to 11 months (with the exception of one sample stored 20 months) before analysis for metalaxyl and up to 20 months before analysis for EBDC and ETU. A DEB review of PP#7F3470/FAP#7H5520 (see March 6, 1987 memorandum of M. Nelson) indicated that metalaxyl and its metabolites were stable for at least 12 months under freezer storage conditions in strawberries, apples, cabbage, lettuce, and potatoes. Accordingly, since samples were stored less than 12 months in all the field trials (including four in California) except for one field trial in California where samples were stored 20 months before analysis, the residue data on metalaxyl stored 12 months or less are valid. [The 18-month data cited by the petitioner were for tobacco, a crop not translatable to grapes.] The following is a summary of information on the storage stability of mancozeb and ETU in apples, tomatoes, and wheat from DEB's Revised Dietary Exposure Analysis for Mancozeb and ETU; Residue Data Submitted in Response to the mancozeb Registration Standard of April 1, 1987 (see August 17, 1989 memorandum of S. Hummel):

> The submitted storage stability data show that mancozeb and ETU are stable up to six months in frozen storage, except for ETU in apples, under the conditions used by the laboratory performing the storage stability study, Enviro-Bio-Tech. These results are not translatable to residue data from other laboratories.

Although the Enviro-Bio-Tech laboratory was also used in this submission for analysis of EBDC and ETU residues, samples were stored longer than 6 months (i.e., samples were stored up to 20 months before analysis). Concurrent storage stability data are not available and accordingly, the grape residue data on EBDC and ETU are not valid since supporting storage stability data are not available.

In summary, the petitioner's proposal for a metalaxyl tolerance with regional registration on grapes is unacceptable (see DEB Comments/Conclusions re: Deficiency Nos. 1c and 1b) and therefore, the over tolerance residues detected for metalaxyl in the California field trials from the

proposed use, cannot be disregarded. Since metalaxyl residues as high as 1.4 ppm were detected in California from the proposed use, a revised Section F raising the proposed metalaxyl tolerance on grapes to 2.0 ppm will also be required unless the petitioner can provide a rationale for disregarding the high value from California.

Deficiency Nos. 4b, 5 and 6 of DEB's March 20, 1986 review are either resolved or are no longer applicable. The residue data requested for the EBDC Special Review have been submitted and are discussed in this review, under Note for EBDC Special Review. Deficiency No. 2 of DEB's October 14, 1988 review has been resolved.

Deficiency No. 7 (Maarch 20, 1986)

At this time, RCB can reach no final conclusion regarding the maximum expected metalaxyl residues in processed grape commodities (i.e., pomace, juice, raisins, and raisin waste) since the adequacy of the 2 ppm grape tolerance cannot be determined without the review of additional residue data generated from California and New York field trials.

Petitioner's Response to Deficiency No. 7

Tables IV and V in Attachment 1 to this review summarize the results for five grape fractionation studies submitted by the petitioner and the following excerpt is the petitioner's narrative response:

"Residue results for processed grape fractions are presented in Table IV. Five fractionation studies were performed, one from a New York location and four from California. Grapes from the New York location were treated with five applications of Ridomil MZ58 at 1.16 lb ai/A/application (or 2.0 lb/A of formulated product) and harvested at 7 days PHI. Samples from a 2X-rate treatment (5 x 2.32 lb ai/A) at the New York location were also fractionated. The four California studies were conducted using four or five applications of Ridomil MZ58 at 1.16 lb ai/A/ application and grapes were harvested with a 7-day PHI. Grapes from one of these four California studies was also treated with the proposed use rate of three applications at 1.45 lb ai plus 1.45 lb ai plus 1.74 lb ai/A and harvested at 66-day PHI (the proposed use directions in this petition). A 2X-rate fractionation study was also conducted for this treatment regime. Maximum residue concentration factors for each fraction are summarized in Table V. The concentration factors, including all available data from Table IV, are calculated using the highest residues in fractions and the lowest residues in fruit. These concentration factors,

therefore, represent the worse-case situation. Considering the differences in test locations (New York vs. California), the variety of grapes, various treatment regimes, and the differences in PHI, the concentration factors in each fraction were consistent. Therefore, the concentration factors from California studies can be applied to food/feed tolerance estimation for the New York study. Based on the maximum concentration factors observed and the proposed 1-ppm metalaxyl tolerance in grapes, the following food/feed tolerances are proposed when grapes are grown in Eastern and Midwestern States using the proposed use directions.

Grape Fractions	Highest Concentration Factor	Proposed Metalaxyl Tolerance
Grapes	--	1
Grace Pomace (Wet and Dry)	4.54X	5
Raisins	3.42X	4
Raisin Waste	6.45X	7

"Note: No residue concentration was observed in juice (0.479X). A tolerance for wine is not required according to the EPA review of PP#6F3362/FAP#6H5493 (RCB Nos. 495 and 496) dated March 20, 1986.

"Data in this report for processed products of grapes from a California study (AG-A 10080) are included to provide mancozeb data (EBDC and ETU) requested by the EPA in their response to PP#6F3362/FAP#6H5493. A label for western grapes is not requested in this petition. This California study also included a treatment regime using five applications of Ridomil MZ58 at 1.16 lb ai/A/application. These data are presented (EBDC and ETU) in response to the EPA request of (S.T. Lewis 'Mancozeb Over Tolerance Residues Reported Under Section 6(a)(2)' March 23, 1989) for the Special Review on mancozeb."

DEB's Comments/Conclusions Re: Deficiency No. 7

Utilizing the lowest residue among multiple fruit samples, and the highest residue in the composited fraction as was done by the petitioner reflects an unrealistic situation. Rather, since two samples (reps) were composited, presumably at equal weight, to single fractionated samples, the average residue in the raw fruit must be compared with the residue in each fraction. This approach indicates maximum concentration factors of < 5X in pomace (dry) and

raisin waste and 3X in raisins. When the petitioner resolves the deficiency pertaining to the 1.4 ppm residue value in raw grapes such that an appropriate RAC tolerance is proposed, appropriate food/feed additive tolerances based on these maximum concentration factors must be proposed.

Deficiency No. 7 remains unresolved.

Deficiency No. 8

At this time, RCB is unable to determine the maximum likely level of secondary residues in animal commodities resulting from established metalaxyl uses and the use on grapes proposed in this petition since a question remains as to the adequacy of the proposed tolerances.

Petitioner's Response to Deficiency No. 8

The petitioner submitted calculations reflecting a theoretical diet with maximum metalaxyl residues based on established and proposed tolerances for cattle and poultry of 20 and 2.3 ppm, respectively.

DEB Comments/Conclusions Re: Deficiency No. 8

Per the following excerpt Residue Chemistry Chapter of the Metalaxyl Registration Standard dated June 22, 1987 the nature of the residue in animals is not adequately understood:

> Presently, the nature of the residue in animals is not adequately understood. On receipt of the data requested in the section entitled "Nature of the Residue in Animals," the appropriate nature of tolerances for residues in animal products will be determined and, with consideration for any newly found metabolites of toxicological concern, the adequacy of the available data regarding the magnitude of the residue in fat, meat, and meat byproducts (except kidney and liver) of cattle, goats, hogs, horses, and sheep will be determined.

Deficiency No. 8 remains unresolved.

Other Considerations

1. Nature of the Residue In Animals

The nature of the residue in animals is not understood. The following excerpt from the Residue Chemistry Chapter of the Metalaxyl Registration Standard dated June 22, 1987 summarizes the status and required studies:

"The nature of the residue of metalaxyl (N-(2,6-dimethylphenyl)-N-(methoxyacetyl)alanine methyl ester) in animals has previously been determined as being inadequately understood for the purposes of establishing permanent tolerances for metalaxyl residues in animal products (refer to the Metalaxyl Guidance Document dated December 1981). The sole ruminant metabolism study discussed in the original Guidance Document failed to characterize ^{14}C-residues in tissues. Additional studies have not been submitted subsequent to issuance of the original Guidance Document. The following data are therefore required:

"o Metabolism studies utilizing ruminants and poultry in which animals must be dosed for a minimum of 3 days with [^{14}C]metalaxyl at a level sufficient to make residue identification and quantification possible. Milk and eggs must be collected twice daily during the dosing period. Animals must be sacrificed within 24 hours of the final dose. The distribution and characterization of residues must be determined in milk, eggs, liver, kidneys and muscle and also skin and gizzard for hen. If the metabolism of metalaxyl in ruminants or poultry is found to differ from that in rats, or with each other, then swine metabolism data may be required. Data reflecting solvent extraction of residues are also required.

"o Representative samples from the above described tests must also be analyzed by current enforcement methods to ascertain the validity of these methods."

2. Analytical Methodology - Residue in Animals

New animal metabolism studies with radiolabeled validation of the proposed analytical methodology are required. Identification of any new metabolites of toxicological concern may require the development of new analytical methodology.

3. Multiresidue Methods

The following excerpt from DEB's review of PP#8F3617/8H5554 (see November 28, 1988 memorandum of F. Griffith) summarizes the remaining multiresidue data currently required:

"In the RCB review of May 13, 1988 by M.J. Nelson for PP#5F3470/FAP#7H5520 - Metalaxyl on Blueberries, Walnuts, Almonds, Almond Hulls, Stone Fruits, Dried Apricots, and Prunes, we had the following conclusions related to MRM data:

> Data have now been submitted on the recovery/behavior of metalaxyl and two of its metabolites (CGA-6286 and CGA-37734) tested through FDA Multiresidue Protocols I through IV of PAM I.

"Note: These data have been forwarded to EPA for publication in a future revision of Appendix I to PAM-I (see letter dated May 17, 1988 by M.J. Nelson to L. Sawyer, FDA [HFF-426]).

> For approval of future metalaxyl tolerances (and to support the continued registration of metalaxyl-containing products), FDA Multiresidue test information must also be supplied for the metabolite CGA-94689.

"In this petition, no MRM data were presented to resolve this deficiency. For a favorable DEB recommendation the petitioner will need to supply the MRM data for metabolite CGA-94689 through each of the four protocols to provide sound defensible reasons why this metabolite cannot be recovered."

4. International Residue Limits

An International Residue Limit (IRL) Status Sheet is appended to this petition review as Attachment No. 3. Codex has a tolerance established for metalaxyl per se of 1 ppm. We note that Codex currently regulates metalaxyl residues in terms of parent only while the U.S. tolerance expression regulates the parent and metabolites containing the 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl) alanine methyl ester each expressed as metalaxyl.

Since the petition review indicates that metalaxyl residues will not exceed 2.0 ppm and since plant metabolism data on grapes (i.e., MRID No. 00071606 per the Residue Chemistry Chapter of the Metalaxyl Registration Standard dated June 22, 1987) indicate that the residue of the parent constitutes 50 percent of the characterized residues which did not include all of the regulated residues in grape juice, no compatibility problems with Codex are anticipated.

Attachments: Two
Attachment No. 1: Summary Tables of Residue Data
Attachment No. 2: International Residue Limit Status Sheet
cc with Attachments: PMSD/ISB, RF, Circu, Metalaxyl Registration Standard File, Reviewer - Otakie, PP#6F3362/FAP#6H5493, Mancozeb Registration Standard File, S. Hummel (DEB), R. Tomerlin (DRES/SACB)
H7509C:DEB:G. Otakie:CM#2:Rm 804:557-7484:MB:11/ /89
RDI:D.Edwards:12/5/89:R. Loranger:12/6/89

53738:I:Otakie:C.Disk:KENCO:11/6/89:dg:vo:ek:vo:dg:vo:dg
R:53763:Otakie:C.Disk:KENCO:12/1/89:dg:vo:ek:dg:sw:vo:dg

Mancozeb/Metalaxyl dietary exposure review

Page _____ is not included in this copy.

Pages 22 through 30 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL METALAXYL

CODEX NO. 138

CODEX STATUS:

☐ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Metalaxyl per se

Crop(s)	Limit (mg/kg)
Grapes	1

PROPOSED U.S. TOLERANCES:

Petition No. 6F3362/6H5493

RCB Reviewer E. OTAKIE

Residue: METALAXYL AND ITS METABOLITES CONTAINING THE 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6-methyl phenyl)-N-(methoxyacetyl) alanine methyl ester

Crop(s)	Limit (mg/kg)
GRAPES	1.0 PPM
WET AND DRY GRAPE POMACE	5.0 "
RAISINS	4.0 "
RAISIN WASTE	7.0 "

CANADIAN LIMITS:

☑ No Canadian limit (on grapes)

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES: