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

FEB 16 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

**MEMORANDUM:**

**SUBJECT:** PP#9F3724/9F03818 - Permanent Tolerance Petitions - New Chemical - Tebuconazole, Fungicide on Peanuts. Evaluation of Amendments Dated August 9, 1991 and February 4, 1992. CBTS Nos. 8877, 8878, 9433 and 9434. MRID Nos. 419802-00 and 422095-01 thru -03,and -05 thru -13 and -20 thru -23; DP Barcodes D170444, D170451, D174886, and D174890.

**FROM:** Gary F. Otakie, P.E., Chemist
Tolerance Petition Section II
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

**THRU:** Debra F. Edwards, PhD., Chief
Chemistry Branch I - Tolerance Support
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**TO:** Susan Lewis, PM 21
Fungicide - Herbicide Branch
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## Background

Mobay has submitted the present Amendments in response to deficiencies outlined in CBTS's May 9, 1991 review of PP#9F3724 concerning the establishment of permanent tolerances for the new chemical tebuconazole.

## Current Submission

## Revised Section F

In the subject Amendment, the petitioner (i.e. Mobay) has provided a revised Section F proposing the following permanent tolerances for the new chemical fungicide tebuconazole (i.e., Folicur, HWG-1608) (alpha-[2-(4-chloro-phenyl)ethyl]-alpha-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol):

| Commodity | Preharvest Interval (Days) | Proposed Tolerance (ppm) |
|---|---|---|
| TOLERANCE PROPOSAL | | |
| Peanuts | 14 | 0.1 |
| Peanut hulls | 14 | 4.0 |
| Peanut hay | 14 | 25.0 |
| FOOD ADDITIVE TOLERANCE PROPOSAL | | |
| Peanut oil | | 0.5 |
| **FEED ADDITIVE TOLERANCE PROPOSAL** | | |
| Peanut meal | | 0.5 |
| Peanut soapstock | | 1.0 |

and for the combined residues of tebuconazole and its 1-(4-chlorophenyl)-4,4-dimethyl-3-(1H-1,2,4-triazole-1-yl-methyl)-pentane-3,5-diol metabolite in the following animal commodities:

| | |
|---|---|
| Eggs | 0.1 |
| Meat, fat, and meat byproducts of poultry | 0.1 |
| Meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep | 0.1 |
| Milk | 0.05 |

The petitioner, per their February 4, 1992 letter, wishes to withdraw without prejudice to a future filing, all commodities in the subject petitions associated with crops grown for seed , wheat, barley and grapes and further to withdraw their application for use of Elite 45 DF for use on grapes and revise their application for use of Folicur 3.6 F by removing the crops grasses grown for seed, wheat and barley. These amendments include a revised Section B and F reflecting these revisions.

An expedited request for temporary tolerances under PP#9G3817 for tebuconazole on peanuts, peanut hulls, peanut oil, and peanut soapstock at 0.1, 4.0, 0.5 and 0.5 ppm respectively has been approved by CBTS (see March 18, 1992 review of G. Otakie). Since the label included a restriction against feeding treated peanut hay/vines to livestock temporary tolerances relating to animal commodities were not required.

**Revised Section B**

The petitioner has submitted a revised label for Folicur 3.6F containing 3.6 lbs tebuconazole per gallon and deleting all uses except peanuts for which the recommended maximum application rate is 8 fluid ounces/A up to a maximum of four applications with a 14 day interval between applications. A maximum of 1 quart (32 fluid ounces) of Folicur 3.6F may be applied per crop season (i.e. 0.9 lb a.i./A or 408.6 g a.i./A) with a 14 day PHI. For optimum control of early and late leaf spots, the lowest recommended rate of a spray surfactant should be tank mixed with Folicur 3.6F. The label also provides for a 6 or 7 treatment program of which only 4 treatments are Folicur 3.6F with the remaining applications of a non-sterol inhibitor fungicide.

**Additional Data**

The submission also included a new peanut metabolism study, revised analytical methods for plants and animals, Independent Laboratory Method Validation for both plants and animals, additional analytical method multiresidue and interference data, new ruminant and poultry feeding studies, new peanut field trials, a new peanut processing study and additional product chemistry data.

**Summary of Deficiencies that Need Resolution**

1. A deferral request is required with a proposed schedule for submission of the TGAI analysis results representing five different production runs of the final full scale process together with a revised CSF with certified limits reflecting these data. The deferral request should be submitted in accordance with the PAG Subdivision D - Product Chemistry, 1982 (see page 50).

2. Submission to the EPA Repository of a standard and Material Data Safety Sheet for the metabolite is required to satisfy 64-1 Sample Submission. (Previous Deficiency No. 6)

3. A successful EPA PMV is required for peanuts. (Previous Deficiency No. 4)

4. A successful EPA PMV is required for animal commodities. (Previous Deficiency No. 8)

5. Additional storage stability data on peanut oil is required. (Previous Deficiency No. 11)

6. In the reports for the crop field trials, the petitioner uses the terms "vines" and "hay". Do they refer to the same commodity? Miles Inc. should clarify how the samples were obtained and provide some indication of their moisture content. Revised Sections B and/or F resolving this issue may be needed depending upon the nature of the samples that were analyzed (Previous Deficiency No. 12).

7. An explanation of the conflicting results of the two peanut processing studies is required. (Previous Deficiency No. 17)

8. Based on the required explanation of the conflicting results of the two peanut processing studies a revised Section F is required. (Previous Deficiency No. 20)

9. A revised Section B proposing a 120 day (4 month) rather than a 33 day crop rotation interval is required per EFGWB/EFED's April 16, 1992 review of B. Conerly concerning the minimum replanting interval supported by current data. (Previous Deficiency No. 2).

**Recommendations**

At this time CBTS recommends against establishing the proposed permanent tolerances for tebuconazole and its t-butyl hydroxy metabolite for the reasons cited under Deficiencies Nos. 1 thru 9 above and discussed in more detail below under "Detailed Considerations".

## Detailed Considerations

The deficiencies cited in CBTS's review of PP#9F3724 (See G. Otakie memoranda of May 9, 1992) will be restated below followed by the Petitioner's Response and CBTS's Conclusions. The numbering of deficiencies follows that of the May 9, 1991 review.

### Deficiency No. 1

A proposed schedule for submission of product chemistry data reflecting the TGAI from the full scale production process is required.

### Petitioner's Response to Deficiency No. 1

The petitioner has submitted additional product chemistry and a revised Confidential Statement of Formula which are contained in **Attachment 1** - The Confidential Appendix.

### CBTS's Comments/Conclusions re: Deficiency No. 1

A detailed discussion is included in Attachment No. 1 (Confidential Appendix). 61-1 Product Identity and Disclosure of Ingredients has been resolved. 61-2 Description of Beginning Materials and Manufacturing Process, 61-3 Discussion of Formation of Impurities, and 62-3 Analytical Method to Verify Certified Limits are tentatively resolved. Any revisions should be forwarded after full scale production commences.

62-1 Preliminary Analysis and 62-2 Certification of Limits are not yet fully resolved but additional data is not required for registration provided the petitioner submits a deferral request in accordance with PAG Subdivision D - Product Chemistry Guidelines October 1982. The deferral request should include an acceptable schedule for submission of analysis results representing five different production runs of the final full scale production process together with a revised CSF with certified limits reflecting these data.

This deficiency although not yet satisfied does not require resolution for registration of tebuconazole provided the petitioner submits an acceptable deferral request.

### Deficiency No. 2

Revised labels for all the proposed product formulations are needed.

### Petitioner's Response to Deficiency No. 2

The petitioner has submitted a revised label for Folicur 3.6F containing 3.6 lbs tebuconazole per gallon and deleting all uses except peanuts for which the recommended maximum application

rate is 8 fluid ounces/A up to a maximum of four applications with a 14 day interval between applications. Folicur 3.6F may be applied in a minimum of 10 gallons of spray solution per acre by ground sprayer or in a minimum of 5 gallons of spray solution per by aircraft spray equipment. A maximum of 1 quart (32 fluid ounces) of Folicur 3.6F may be applied per crop season (i.e. 0.9 lb a.i./A or 408.6 g a.i./A) with a 14 day PHI. For optimum control of early and late leaf spots, the lowest recommended rate of a spray surfactant should be tank mixed with Folicur 3.6F. The label also provides for a 6 or 7 treatment program of which only 4 treatments are Folicur 3.6F with the remaining applications of a non-sterol fungicide.

**CBTS's Comments/Conclusions re: Deficiency No. 2**

CBTS's notes that the petitioner has deleted all proposed tebuconazole uses except peanuts. A revised Section B proposing a 120 day (4 month) rather than a 33 day crop rotation interval is required per EFGWB/EFED's April 16, 1992 review of B. Conerly concerning the minimum replanting interval supported by current data and further revisions relating to the peanut vine/hay issue may also be required (see Deficiency Nos. 6 and 9).

This deficiency is not resolved.

**Deficiency No. 3**

Additional data on the wheat and grape metabolism studies are required.

**Petitioner's Response to Deficiency No. 3**

The petitioner per their February 4, 1992 letter wishes to withdraw without prejudice to a future filing, all commodities in the subject petitions associated with crops grown for seed, wheat, barley and grapes and further to withdraw their application for use of Elite 45 DF for use on grapes and revise their application for use of Folicur 3.6 F by removing the crops grasses grown for seed, wheat and barley. These amendments include a revised Section B and F reflecting these revisions.

**CBTS's Comments/Conclusions re: Deficiency No. 3**

Since proposed permanent tolerances on wheat and grapes have been withdrawn, this deficiency is no longer applicable to the current proposed use on peanuts.

This deficiency is resolved.

**Deficiency No. 4**

A new peanut metabolism study, radiolabeled validation of proposed analytical methodology, and a successful EPA PMV are required for peanuts.

**Petitioner's Response to Deficiency No. 4**

The petitioner has submitted a new peanut metabolism study:

Metabolism of (Chlorophenyl-UL-14C) Tebuconazole in Peanuts, June 1, 1991: MRID # 419802-01

In summary peanut plants were treated with 45DF (tebuconazole; Chlorophenyl-UL-14) as foliar spray at the rate of 204 g a.i./acre to peanut plants at 6, 9, 11, 13, 15, 17, and 19 weeks after planting and was equivalent to 3.5X the recommended treatment rate. All tissue samples (forage and pods) were allowed to air dry for 4 days prior to processing. At harvest (2 weeks following the last application) the total radioactive residue in the forage, shells and kernels was 110, 17.7 and 0.545 ppm, respectively. Peanut forage, shells and kernel samples were pulverized in either dry ice or liquid nitrogen transferred into marked plastic bags and placed in a freezer at -24 C. To assure the integrity of peanut samples, initial extractions were performed from 16 to 51 days after harvest, and again at later intervals up to 154 days after harvest.

The extraction scheme used for the peanut kernels was based on the analytical residue method for tebuconazole and a lipid extraction scheme. In summary, peanut kernels (25 g) were homogenized in 400 ml of acetone/water (3:1) and the rinse was vacuum filtered and the filtrate was radioassayed. The acetone/water filtrate was partitioned against 100 ml of methylene chloride with sodium chloride added to aid in separation and the aqueous phase again partitioned with methylene chloride and both the organic and aqueous phases radioassayed. The organic phases were combined and concentrated to dryness using acetonitrile and the dry residue was dissolved in methanol, radioassayed and subjected to TLC and HPLC analysis.

The aqueous fraction following partitioning with methylene chloride was subjected to a 1N HCL reflux for 4 hours partitioned with methylene chloride and ethyl acetate and concentrated to dryness using acetonitrile and the dry residue radioassayed dissolved in methanol radioassayed, and subjected to TLC and HPLC. Solids remaining following the acetone/water extraction were homogenized twice in hexane and the extracts combined and radioassayed.

The hexane extract was concentrated to an oily residue and dissolved and partitioned with hexane/acetonitrile followed by further partitioning and base hydrolysis. Solids remaining following extraction with hexane were further extracted with chloroform/methanol and radioassayed. Solids remaining after this extraction were subjected to a 1N HCL reflux for four hours and the hydrolyzate partitioned with ethyl acetate and both the ethyl acetate and organic phases radioassayed.

In summary, for characterization of radioactive residues in the peanut kernel, the extracted radioactivity was separated into an organosoluble fraction and an aqueous fraction containing 21 and 18 % of the total radioactivity, respectively. HPLC analysis of the organosoluble radioactivity identified a majority of this activity as tebuconazole. Subjecting the aqueous fraction to a 1N HCL reflux for four hours failed to render a substantial amount of the radioactivity organosoluble (1%). Solids remaining following extraction with acetone/water were further extracted with hexane which extracted an additional 30% of the total radioactivity, which did not significantly partition into acetonitrile thus indicating the absence of unconjugated tebuconazole and t-butylhydroxy analog residues. Partitioning the hexane fraction against sodium bicarbonate failed to trap any of the radioactivity in the sodium bicarbonate thus indicating the absence of any components containing the free acid group.

The lipid containing hexane fraction was concentrated and saponified to hydrolyze any acidic tebuconazole-derived residues that may have conjugated with glycerol via the ester linkage and partitioning the hydrolyzate with hexane failed to render any substantial amount of the radioactivity organosoluble thus indicating the absence of long-chain alcohols or saponified material. After acidification of the hydrolyzate nearly all the radioactivity (27%) was extracted into hexane, indicating that the radioactive residues were **probably** fatty acids. Attempts to concentrate this fraction resulted in the sample solidifying at room temperature. Although TLC of the extract was difficult, after derivatization with diazomethane the radioactivity chromatographed directly with the coextractives and appeared to have a Rf value (i.e. chromatographed to the same region) similar to the Rf value for oleic acid (9-octadecenoic acid). Further extraction of the hexane-extracted solids with methanol/chloroform released an additional 4% of the total radioactivity which were characterized as bound lipids.

Acid hydrolysis of the extracted solids with 1N HCL released a majority of the remaining radioactivity (23%), but only 5% of the total activity was organosoluble. In summary for the peanut kernels 19% of the total radioactivity was identified as unmetabolized tebuconazole, 4% was associated with complex lipid material, 9% was unidentified organosoluble material, 34% was characterized as polar aqueous material, 4% was unextractable following acid hydrolysis and 30% was lipophilic in nature and appeared to be incorporated into naturally occurring fatty acids.

Further extraction of a hexane extracted solids nutmeat sample (i.e. non-extractable residue) with 1 N HCL reflux for four hours resulted in extraction of 36% of the total radioactivity from the peanut kernel solids. The radioactivity in the hydrolysate was polar in nature and only 8% of the total radioactivity was organosoluble and characterized in one of five of the extractions, resulting in four radioactive peaks identified as tebuconazole 1%, t-butylhydroxy analog 4%,

hydroxyphenyl analog 1%, and an unknown metabolite 2% (included in Attachment as Table 7 from the report).

In order to extract peanut oil the peanut kernels were extracted overnight (18 hours) resulting in extraction of 32 to 34% of the kernels weight being extracted from the peanuts. This extraction resulted in an apparent quantitative extraction of peanut oil from the kernel (i.e. based on an average yield of 35% peanut oil obtained during commercial processing). The peanut oil contained radioactive residue concentrations of 0.480 ppm to 0.517 ppm compared with residues of 0.545 ppm in the whole kernel. Radioactive residues were not concentrated in the peanut oil.

The characterization of radioactive residues in peanut shells and foliage followed slightly different extraction schemes. In the peanut forage 70% of the total radioactivity was identified as tebuconazole, 7% was the t-butylhydroxy analog and 1% was the hydroxyphenyl analog; 13% was unidentified organosoluble material; 3% was aqueous; and 6% was characterized as unextractable following acid hydrolysis. The unidentified organosoluble material was composed of at least seven radioactive components. In the peanut shells 58% of the total radioactivity was identified as tebuconazole, 4% was the t-butylhydroxy analog and 1% was the hydroxophenyl analog; 10% was unidentified organosoluble material; 5% of the total radioactivity was characterized as aqueous; and 22% was characterized as unextractable following 6N HCL. The unidentified organosoluble material was composed of at least 10 radioactive components.

Tables 4, 5, 6 containing the distribution of radioactive residues for peanut forage, shells and nutmeat and Table 7 summarizing the results of five individual extractions, Figure 25 a pie diagram for peanut nutmeat, and Figure 26 with the proposed metabolic pathway for tebuconazole in peanuts from the study, are provided collectively and in their entirety as **Attachment 2** to this review.

The petitioner concluded that tebuconazole was the major radioactive component identified in the peanut forage (70%) and shells (58%) and the t-butylhydroxy analog was also identified in the peanut forage (7%) and shells (4%). The t-butylhydroxy analog was found in the form of a glucoside conjugate in the aqueous fractions and was released following a 4 hour reflux with 1N HCL. In the peanut shell, 22% of the total radioactivity was not extractable even after refluxing with 6N HCL.

In summary, unmetabolized tebuconazole was identified in peanut kernels and accounted for approximately 13 to 19% of the total radioactivity. A small amount (4%) of the t-butylhydroxy analog was identified following acid hydrolysis of hexane extracted solids. Approximately 29 to 34% of the total radioactivity in the peanut kernel was lipophilic and appeared to result from the incorporation into naturally occurring fatty acids.

Based on this metabolism study and as well as previously submitted plant metabolism studies in peanuts, wheat and grapes the **petitioner** believes that the total toxic residue of tebuconazole for the tolerance expression purposes in peanuts (forage, shells, or kernels) should be defined as tebuconazole, which constitutes the major residue in all matrices. The t-butylhydroxy analog which represented less than 10% of the total radioactive residue in any of the peanut tissues should not be included in the tolerance expression. From a toxicological perspective, this alcoholic analog, which has been shown to account for 16 to 28% of the total radioactivity in urine from rats treated with C14 tebuconazole, should be no more toxic than the relatively non-toxic tebuconazole. The total toxic residue (tolerance expression) in grapes and wheat treated with tebuconazole has already been determined by EPA to consist of tebuconazole itself.

**CBTS's Comments/Conclusions re: Deficiency No. 4**

This third peanut metabolism study conducted at an exaggerated application rate responds to deficiencies in the two peanut metabolism studies previously submitted. Although only approximately 25% of the TRR was identified (including 20% parent and 4% the t-butylhydroxy metabolite) significant efforts were made to characterize and identify bound residues. A December 15, 1992 HED Metabolism Committee Meeting on tebuconazole concluded that for the current proposed use on peanuts inclusion of the HWG 2061 metabolite in the tebuconazole tolerance expression was not required since its toxicity was expected to be similar to the parent, it accounted for less than 10% of the TRR, and it would be expected to be present at very low or non-detectable levels based on the amount of parent found in the field trials.

The nature of the residue in peanuts is adequately understood. The residue of concern consists primarily of the parent tebuconazole. Therefore the tolerance expression for tebuconazole on peanuts (i.e. nutmeat, shells, forage, oil, meal and soapstock) will include the parent only.

This deficiency is resolved.

**Deficiency No. 5**

Additional experimental data on the poultry and ruminant metabolism studies are required.

**Petitioner's Response to Deficiency No. 5**

The petitioner has responded to several specific deficiencies iterated in CBRS reviews of PP#9G3817 (see C. Olinger review of June 8, 1990, S. Hummel review of December 9, 1991, and B. Cropp-Kohlligan review of March 6, 1992). The CBRS comments and corresponding petitioner responses are presented below followed by our (CBTS) final conclusion.

Addendum I - The Metabolism of 14C-Folicur in Chickens
Response to EPA Requests and Inquiries: MRID # 421558-01

CBRS Comments/Petitioner's Response

CBRS Comments

This deficiency remains outstanding. The amended report raises additional questions. The results of the study have been revised. Different figures are presented for the total radioactive residue, with no explanation, and insufficient data to verify the calculations. Some of the tabulated results are higher and some are lower than previously reported. The metabolism study should contain sufficient data along with a complete sample calculation so that we may verify the petitioner"s calculations. Mobay should submit a complete copy of the poultry metabolism report, along with complete supporting calculations.

Response

"Several extractions were performed during the initial tissue analysis. Each of these extractions were preceded by total tissue residue analysis. The raw data for the results presented in the amended report were easily located, hence could be readily verified." The petitioner provided data tables containing the residue levels (dpm) in tissues/organs (i.e. liver, kidney, gizzard, heart, fat, skin, muscle and egg) tissue weights, and sample calculations used to determine the ppm residue levels after multiple dose administration of 14C Folicur to five chickens.

CBRS Comments

We also noticed a discrepancy between the ratio of radiolabeled tebuconazole and metabolites in poultry liver extract. The peak sizes in the HPLC radiochromatogram (Figure 6) do not match the tabulated results in Table 4 of the previous submission. The peak ratios for the kidney extract (Figure 7) have the same relative ratio as previously tabulated results. This discrepancy must be explained. Calculations must be provided to support all results.

Response

"The metabolite distribution in organic extracts of tissues/organs (Table 4 of Mobay Report No. 87156) was obtained from TLC analysis. The bands corresponding to Folicur or each metabolite were individually scrapped and quantitated by liquid scintillation counting. Metabolite identification was also achieved by co-chromatography and/or mass spectrometry of extracts from the TLC bands. The HPLC radiochromatograms presented in the report serve as additional or confirmatory identification. Since the TLC analysis afforded better separation of metabolites, quantification of metabolites based on

TLC data was used as being more accurate." The petitioner provided copies of sample TLC radiochromatograms and indicated that the relative band intensities/size for each chromatogram closely match the tabulated results in Table 4 discussed above.

Addendum II - The Metabolism of 14C Folicur in Chickens Additional Response to EPA Requests and Inquiries: MRID No. 422095-04

CBRS Comments/Petitioner's Response

CBRS Commehts

Data are presented in the following table (ppm tissue residue levels and percent distribution of metabolites in tissues, Table 4, page 18, of Miles Report No. 87156). No calculations could be confirmed since tissue weights, dpm and ppm values were not included. Sample calculations were not provided.

Response

"The report on the Metabolism of 14C-Folicur in Chickens (Miles Report No. 871156) was revised to correct the ppm values for the total residue levels and include tissue analysis dates and standard deviation values in Table II (page 16). Appropriate ppm value changes in the Abstract (page 8), Results and Discussion (page 12), and Conclusions (page 13) were made to reflect the corrected values.

Addendum I of the chicken metabolism report (Miles Report No. 87156-1) included the tissue weights, dpm, and ppm values. In addition, sample calculations for ppm residue level, calculated as ppm tebuconazole equivalents, were provided in Addendum I.

CBRS Comments

The calculations provided for minimum sensitivity of 14C assay listed a different specific activity for the plasma samples. This discrepancy should be clarified.

Response

"As stated in the preparation and administration of dose section of the chicken metabolism report (page 9 of Miles Report No. 87156), the multiple dose study utilized 14C Folicur with a specific activity of 10.9 mCi/mmole (75463 dpm/ug). Although not stated, the plasma level or single dose study utilized undiluted 14C Folicur with a specific activity of 20.08 mCi/mmole (144827 dpm/ug)."

CBRS Comments

The Report states the in-life phase was completed in February, 1985 and characterization in November, 1987. Storage

stability data were submitted to demonstrate stability during this period and are discussed in the Storage Stability section of this review. These data do not include stability up to 33 months.

Although storage stability data are presented, it could not be determined from the data provided whether the tissues were analyzed within the acceptable period.

Response

"Although the qualitative analysis involving metabolite characterization and/or identification were not completed until 33 months after sacrifice, the quantitative data presented for the total tissue residue levels, the percent distribution of radioactivity in the extracts and extracted solids, and the metabolite distribution in tissues (Tables II, III and IV, Miles Report No. 87156) should not change for the following reasons:

Tissue analysis for the quantitation of metabolites (metabolite distribution in tissues except for eggs) and the total tissue residue levels were performed within 3 months after the in-life had been completed. The revised stability report (Miles Report No. 98420, MRID 42125801) in support of the poultry metabolism study indicates that the metabolites are stable for at least 3 months.

An additional storage stability study (Miles Report No. 101340, MRID 42125801) indicates that Folicur and HWG 2061 are stable for at least 3 months.

An additional storage stability study (Miles Report No. 101340, MRID 42125801) indicates that Folicur and Hwg 2061 are stable in eggs for 12 months under freezer conditions.

CBRS Comments

Deficiencies in the storage stability study must be clarified. The residue concentrations at each interval must be reported and explanation for increases in relative percentages over the storage interval must be provided.

Response

The storage stability study (Miles Report No. 98420, MRID 421125801) was revised to include ppm levels of metabolites (Table I) and to add the appropriate ppm value changes in the Abstract (page 7), Results and Discussions (page 9), and Conclusions (page 10) to reflect the corrected values. In addition, the stabilities of the parent and metabolites were clarified in the corrected report. The Results and Discussion section (page 10 of Miles Report No. 98420) was also revised to explain the increases in relative percentages over the storage interval.

CBRS Comments

As outlined in the Subdivision O Data Reporting Guidelines, the weights of the animals, food consumption, and egg production should be provided. If the consumption and production are abnormal, possible explanations should be discussed.

Response

"Although the individual bird weights cannot be located in the available notebooks, the average weight of the chickens was recorded as 1.1 kg. The dose administered to the birds was calculated on the basis of the average weight. Each of the five chickens, therefore, received the same dose of Folicur. The tissues were composited before analysis, hence the tissue residue levels and distribution of metabolites indicated in the report reflect any differences that may have occurred in individual chickens.

There are no records to indicate what the feed consumption or egg production was during the 3-day metabolism study. Since the dose was administered by capsule and was based on body weight, the actual amount of feed consumed was probably not considered vital by the author. In like manner, since eggs were obtained for analysis, the production per day was probably just overlooked and no formal record was kept.

This poultry metabolism study was conducted and written (January, 1988) before the Subdivision O Data Reporting Guidelines (October,1988) were issued by EPA, hence the author did not have the benefit of the DRG when he prepared the report.

CBRS Comments

The dpm and ppm values for the tissues/organs should be tabulated so DEB may confirm some calculations. Sample calculations and the data from the single dose study should be included as well

Response

The dpm and ppm values as well as sample calculations to determine the later have been given in Addendum I for the Metabolism of 14C Folicur in Chickens (Miles Report No. 87156-1).

The petitioner also provided additional tables with the radioactivity (dpm/ml) in whole blood and plasma taken from five chickens dosed at 1.0 mg/kg with 14C Folicur.

CBRS Comments

Also, based on this data, the petitioner should estimate the feeding level (PPM) that the 10 mg/kg/day dosing level is

equivalent to, so a comparison to residue levels detected in the poultry feeding study can be made.

Response

The average weight of chicken used in the metabolism study was 1.1 kg. At the 10 mg/kg dosing level, each bird received 11 mg of Folicur/day. Assuming each bird consumes 5% of its body weight/day, the daily food intake would be 55 g. The dose given to each chicken/day (11 mg) in 55 g of feed would correspond to 200 ppm.

**CBTS's Comments/Conclusions re: Deficiency No. 5**

The petitioner's response to the above deficiencies is adequately addressed in the two Addenda submitted for the poultry metabolism study.

The nature of the residue in poultry and ruminants is adequately understood and the primary residues are tebuconazole and its t-butylhydroxy metabolite (HWG2061).

This deficiency is resolved.

**Deficiency No. 6**

Additional product chemistry data on the TGAI (i.e., 63-5, 63-13, 64-1) are required.

**Petitioner's Response to Deficiency No. 6**

The petitioner submitted the following report:

Supplement 1 Product Chemistry of Folicur Technical; By T. D. Talbott; December 9, 1991; MRID No. 40700903.

The following data were included:

63-5 Melting Point, C: PAI: 104.7
TGAI: 102 - 103 Uncorrected
Thomas Hoover Uni-Melt
Capillary melting point apparatus

63-13 Storage Stability: The petitioner has revised the label for Technical Folicur to include a restriction against packaging Technical Folicur in metal containers. Therefore additional data on the storage stability of the technical in metal containers is not required.

64-1 Sample Submission: The petitioner indicates that a 200 gram sample of Mobay process technical with a purity of 95.6% was submitted on 11/13/91 with a requested arrival of 11/19/91. Also five grams of a characterized reference standard (88R11-26) with

a purity of 94.7% was submitted on 12/15/89 and scheduled to arrive 12/22/89.

Data previously discussed in CBTS's May 9, 1991 review of PP#9F3724 on 63-8 Solubility, 63-9 Vapor Pressure, and 63-11 Octanol water partition coefficient were also included in the report.

**CBTS's Comments/Conclusions re: Deficiency No. 6**

A 1/25/93 check with Patricia Beyer with the EPA Chemical Standards Repository in RTP, North Carolina indicated that although a standard for tebuconazole with a Material Data Safety Sheet has recently been received (i.e. 1/93) a standard for the metabolite has not yet been received.

Submission to the EPA Repository of a standard and Material Data Safety Sheet for the metabolite is required to satisfy 64-1 Sample Submission.

This deficiency is not yet resolved.

**Deficiency Nos. 7 and 18**

7. Revised copies of the proposed analytical methodology for residues of tebuconazole in plants radiolabeled method validation and a successful EPA PMV are needed.

18. Revised analytical methodology for tebuconazole and significant metabolites in peanut oil and soapstock is required.

**Petitioner's Response to Deficiency Nos. 7 and 18**

The petitioner has submitted the following studies:

Gas Chromatographic Method for Determination of Residues of Tebuconazole in Crops, Processed Products, Soil and Water; Report No. 101341, W. Maasfeld, January 15, 1992, MRID No. 422095-05

The previous analytical method (i.e. No. 94295) has been revised to incorporate recommendations made in the independent laboratory method validation of the method. These revisions involve extraction, cleanup and gas chromatography procedures. Also revised extraction procedures for processed peanut products are included.

Extraction of residue of tebuconazole from grain and peanuts (kernels, foliage and hay/straw) includes an initial homogenization of the samples in acetone/water (3:1). In the case of peanut shells they are finely ground and subjected to overnight reflux in acetone/water (3:1). The resultant acetone/water extract is saturated with sodium chloride, and the tebuconazole residue is partitioned into dichloromethane.

The revised method includes different extraction procedures for tebuconazole in processed peanut products. Extraction of the tebuconazole residue from refined and crude peanut oil involves extraction with hexane followed by partitioning the residue of tebuconazole into acetonitrile. Soapstock is extracted with ethyl acetate. and the ethyl acetate is partitioned sequentially against 1N aqueous HCL and water. Residue of tebuconazole partitioning into ethyl acetate are further purified using a hexane/acetonitrile cleanup.

With the exception of peanut shells, all plant extracts are purified using gel permeation chromatography and silica gel chromatography. Peanut shell extracts are subjected to an acetone precipitation procedure. With the exception of peanut oil, extracts are further purified using either an SPS HPLC column or a C-18 Bond Elut column prior to gas chromatography with a nitrogen/phosphorous detector.

A confirmatory GC procedure is also included. The following table summarizes the results of the two methods:

| Matrix | Fortification PPM | Percent Recovery of Methods | |
|---|---|---|---|
| | | Confirmatory | Primary |
| Peanut meat | 0.05 | 108 | 118 |
| oil (refined) | 0.05 | 94 | 80 |
| oil (crude) | 0.05 | 82 | 90 |
| meal | 0.05 | 98 | 86 |
| soapstock | 0.05 | 86 | - |
| dry hay | 5.00 | 82 | 98 |
| shells | 0.10 | 101,82 | 80, 109 |

Extraction Efficiency of the Analytical Residue Method for Tebuconazole in Crops; Report No. 101342, R. G. Minor and P.L. Freeseman, October 7, 1991; MRID No. 422095-7.

The extraction efficiency of the analytical residue method for detecting tebuconazole in crops was evaluated with matrices containing aged radioactive residues from C14 tebuconazole peanut and wheat metabolism studies. The extraction efficiency of the analytical method was found to be 80 to 107, 103, 98, and 96%, for peanut forage, shells, nutmeat and wheat straw, respectively. An overnight reflux in the recommended extraction solvent(acetone/water) was necessary to increase the extraction efficiency in peanut shells from 62-63 to 107%.

The Independent Laboratory Method Validation for the Analysis of Tebuconazole (FOLICUR) in Crops and Processed Products; Report No. 101991; M. E. Bajzik; MRID No. 422095-6.

Huntingdon Analytical Services in Middleport, N. Y. was selected to validate the analytical residue procedure for determination of tebuconazole residues in peanut shells, peanut oil, and soapstock. The analytical method in Miles Report No. 101341 was used and the control values were <0.1 ppm for shells and soapstock and <0.05 ppm for peanut oil. Minor method modifications were made including increasing the chromatography time to allow for late eluting peaks and using isothermal GC conditions for all three matrices. The required time to complete a set of eight sample was estimated at 10 man hours over a three day period for peanut oil. 21 man hours over a four day period for soapstock, and 15 man hours over a four day period for peanut shells.

| Matrix | Fortification-PPM | Recovery (Avg) % |
|---|---|---|
| Peanut Shell | 2 or 1X | 88, 94 (91) |
| | 10 or 5X | 102, 112 (107) |
| Peanut Oil | 0.1 or 1X | 74, 91 (82) |
| | 0.5 or 5X | 87, 102 (94) |
| Peanut Soapstock | 0.3 or 1X | 70, 76 (73) |
| | 1.5 or 5X | 98, 116 (107) |

The petitioner concluded that Huntington Analytical Services successfully performed the independent laboratory validation of the analytical method for tebuconazole residues in peanut shells, oil and soapstock.

**CBTS's Comments/Conclusions re: Deficiency Nos. 7 and 18**

Independent Laboratory Method Validation for the proposed analytical methodology for peanuts has been successfully completed and a revised copy of the proposed analytical methodology submitted. The proposed analytical methodology will be forwarded to EPA Laboratories for the EPA PMV once the EPA Repository confirms that analytical standards are available.

A decision on this deficiency is deferred pending the results of the EPA PMV.

This deficiency is not yet fully resolved.

**Deficiency No. 8**

Revised enforcement analytical methods for residues of tebuconazole and its hydroxy metabolites (HWG-2061) in animal matrices, radiolabeled method validation, an independent method validation, and a successful EPA PMV are required.

**Petitioner's Response to Deficiency No. 8**

The petitioner has submitted a revised analytical method for animal matrices and independent laboratory method validation.

An Analytical Residue Method for the Determination of Tebuconazole and HWG 2061 Residues in Bovine and Poultry Tissues, Milk and Eggs; R. R. Gronberg et. al., Mobay Report No. 10136; October 14, 1991; MRID No. 422095-10

A revised analytical method has been developed to determine tebuconazole and its t-butyl hydroxy metabolite (HWG 2061) in animal tissues and eggs. The matrices are extracted by the scheme used in the metabolism experiments, and the extracted conjugated HWG 2061 is hydrolyzed by an overnight acidic reflux. After hydrolysis, tebuconazole and HWG 2061 residues are separated from the sample matrix by gel permetation chromatography, hexane/acetonitrile partitioning and high performance liquid chromatography, hexane/acetonitrile partitioning and high performance liquid chromatography using both reverse phase and semipermeable surface columns. Tebuconazole and a t-butyldimethylsilane derivative of HWG 2061 are each analyzed using a medium-polarity capillary gas chromatography column and a nitrogen specific flame ionization detector. The limit of determination for tebuconazole and HWG 2061 is 0.1 ppm in bovine and poultry tissues and eggs and 0.05 ppm in milk.

Because of overnight hydrolysis, lengthy cleanup procedures, and derivatization prior to analysis, this method takes approximately 4 days to complete a set of six samples. The petitioner indicated that eight different individuals have successfully run this method and recorded acceptable method recoveries.

The recoveries of tebuconazole and HWG 2061 obtained using the analytical method are summarized in the following table:

| Matrix | Compound | Fortifica. PPM | Recovery % |
|---|---|---|---|
| **Bovine** Liver | Tebuconazole | 0.10 | 89, 91 |
| " " | HWG 2061 | " | 72, 78 |
| " Kidney | Tebuconazole | " | 76, 78 |
| " " | HWG 2061 | " | 77, 89 |
| " Muscle | Tebuconazole | " | 91, 101 |
| " " | HWG 2061 | " | 89, 81 |
| " Fat | Tebuconazole | " | 91, 94 |
| " " | HWG 2061 | " | 87, 78 |
| " Milk | Tebuconazole | 0.10 | 94, 101 |
| " " | " | 0.05 | 105, 106 |
| " " | HWG 2061 | 0.10 | 102, 102 |
| " " | " | 0.05 | 83, 93 |
| **Poultry** Liver | Tebuconazole | 0.10 | 98, 90 |
| " " | HWG 2061 | " | 95, 86, 117 |
| " Muscle | Tebuconazole | " | 116, 113 |
| " " | HWG 2061 | " | 114, 94 |
| " Fat | Tebuconazole | " | 87, 89 |
| " " | HWG 2061 | " | 74, 92 |
| " Skin | Tebuconazole | " | 96, 106 |
| " " | HWG 2061 | " | 95, 95 |
| " Eggs | Tebuconazole | " | 87, 91 |
| " " | HWG 2061 | " | 86, 71 |

Independent Laboratory Validation of the Analytical Residue Method for Tebuconazole and HWG 2061; By M.E. Krolski et.al.; September 27, 1991; MRID No. 422095-12.

An independent laboratory method validation of the analytical method discussed above (i.e. Mobay Report 101348) was performed to determine residues of tebuconazole in bovine liver and milk. The independent laboratory validation was done by the **petitioner** at Mobay Research Park located near Stillwell, Kansas. A total of 18 analyses were performed. The standard GC conditions were used in this analysis and control samples showed no interference (0.02 ppm) at the tebuconazole and HWG 2061 retention times. Linearity curves for tebuconazole and HWG 2061

showed a linear response from 0.5 ppm to 4.0 ppm. The following table summarizes the results obtained:

| Matrix | Compound | Fortific. PPM | Recovery % |
|---|---|---|---|
| Bovine Liver | Tebuconazole | 0.10 | 71, 82 |
| " " | " | 0.50 | 93, 117 |
| " " | HWG 2061 | 0.10 | 89, 109 |
| " " | " | 0.50 | 92, 95 |
| " Milk | Tebuconazole | 0.10 | 91, 107 |
| " " | " | 0.50 | 86, 94 |
| " " | HWG 2061 | 0.10 | 82, 103 |
| " " | " | 0.50 | 84, 92 |

The time for analysis was estimated at 37 person-hours, over a period of 5 calendar days, to spike, process, analyze and evaluate the data for one set of six samples.

Although the independent method validation was also done at one of the petitioner's labs, the only contact between the two labs prior to completion of the method validation was a telephone conversation following the initial unsuccessful liver method validation. The telephone conversation was followed by receipt of a revised method, using a different gpc cleanup procedure which resulted in validation of the method.

Extraction Efficiency of the Analytical Residue Method for Tebuconazole and HWG 2061 in Animals; Report No. 101339; By L. Fought; October 9, 1991; MRID No. 422095-11.

To show that the aged total toxic residues of concern which were reported in the goat and metabolism studies are efficiently extracted by the revised analytical method (Report No. 101316), the same radiolabeled samples from the goat metabolism study were extracted by this method. The goat tissues and milk were extracted to verify the quantities of tebuconazole and HWG 2061 after prolonged storage. Since an insufficient quantity of tissue remained from the chicken metabolism study C14 poultry samples were obtained from another set of chickens dosed with C14 tebuconazole.

The results are summarized in the following table by comparing the extraction efficiency obtained in the metabolism/method studies (tissues extracted by the metabolism study procedure included no acid hydrolysis while tissues extracted by the analytical method did include acid hydrolysis).

| Tissue | Tebuconazole % Eff. Method/Metabol | HWG 2061 % Eff. Eff. Method/Metabol |
|---|---|---|
| Liver (Goat) | 113 (0.78/0.69) | 76 (2.60/3.44) |
| " (Poultry) | 137 (0.63/0.46) | 49 (4.47/9.05) |
| Kidney (Goat) | 330 (0.76/0.23) | 78 (2.59/3.33) |
| Muscle (Goat) | >100 (.01/.00) | 75 (0.03/0.04) |
| " (Poultry) | 133 (0.12/0.09) | 92 (0.12/0.13) |
| Fat (Goat) | 500 (0.05/0.01) | 108 (0.12/0.13) |
| " (Poultry) | 124 (4.70/3.78) | 118 (0.52/0.44) |
| Eggs | 100 (0.83/0.83) | 108 (0.56/0.52) |
| Milk | >100 (0.01/0.00) | 50 (0.03/0.06) |

For the goat tissues and milk the quantity of tebuconazole extracted was greater (>100% to 500%) than the quantity extracted in the metabolism study procedure but the HWG 2061 was less than extracted in the metabolism study procedure (50%). Also, the analytical residue method extracted tebuconazole from goat kidney, muscle, fat, and milk more efficiently than the metabolism procedure. The acid hydrolysis of the extract may have caused this increase in efficiency. The residues extracted using the analytical residue method on poultry matrices appeared comparable to those obtained from the metabolism study procedure except for liver (49%). The source of the inefficiency in the extraction of poultry liver could not be determined since insufficient tissue was available for further analysis. Overall, the sum of the tebuconbazole and HWG 2061 residues extracted by the analytical residue method was comparable to that extracted by the metabolism procedure. In general, the residue values obtained using the analytical residue method tend to be on the high side.

**CBTS Comments/Conclusions re: Deficiency No. 8**

CBTS notes that both the method validation and the independent laboratory validation were done at different laboratories in the petitioner's organization. The petitioner has certified that the only contact between the two labs was a telephone conversation to discuss the initial unsuccessful method validation for liver which resulted in method revisions with subsequent adequate successful validation. PR Notice 88-5 concerning Independent Laboratory Confirmation states " The laboratory chosen to conduct the confirmatory trial must be unfamiliar with the method, both in its development and subsequent use in analyzing field samples. Provided this criteria is met, the laboratory chosen to conduct the

confirmatory trial may be in the petitioner's organization." Since the petitioner has certified that the only contact between the two laboratories was a telephone conversation to discuss problems with the initial method validation for liver, these criteria were satisfied.

The method recoveries obtained for both the method validation and independent method validation for tebuconazole and its t-butylhydroxy metabolite (HWG-2061) appear acceptable. The higher residues obtained for goat liver and milk from the proposed method than obtained in the Extraction Efficiency Study from the metabolism method procedure may be partially caused by the lack of acid hydrolysis in the metabolism method. However, although total residues in milk may be comparable, tebuconazole residues were higher while HWG 2061 residues were lower. CBTS notes that although the analytical procedure used in the goat metabolism study (i.e. Lee and Wood) did include acid hydrolysis of extracts the metabolism study procedure used in the above discussed extraction study did not include acid hydrolysis. Since the analytical methodology used in the feeding studies included acid hydrolysis, proposed tolerance levels include conjugated residues. CBTS notes that the method is relatively long and requires approximately one week to complete. The proposed analytical method will be forwarded to EPA Laboratories for EPA Petition Method Validation (PMV) once samples of the analytical standards for tebuconazole and HWG-2061 are available at the EPA Repository.

A final decision on this deficiency is deferred pending successful completion of an EPA PMV.

This deficiency is not yet fully resolved.

**Deficiency No. 9**

Additional data on the submitted interference studies and appropriate confirmatory methods are required.

**Petitioner's Response to Deficiency No. 9**

The petitioner has submitted the following study.

A Competitor Product Interference Study for the Analytical Residue Method for Tebuconazole Residues in Plants; Report No. 95680-1, R. R. Gronberg, October 14, 1991; MRID No. 422095-7.

As of January, 1987, 94 nitrogen and/or phosphorous containing compounds had a registered tolerance on wheat, grapes, barley, peanuts, or seed grasses. An additional interference study was conducted to investigate the 25 compounds which have been granted a tolerance since January 1987. Of the 25 compounds tested in this study, only nitralin gave a response near the retention time for tebuconazole using the gas chromatographic procedure. When nitralin was reanalyzed using the confirmatory

gas chromatographic procedure, nitralin did not interfere with the analysis of tebuconazole. In conclusion of 121 nitrogen and or phosphorous containing compounds (except two which were unavailable for testing) with registered tolerances in wheat, grapes, barley, peanuts or seed grasses, none interfered with the analysis of tebuconazole under the conditions described in the analytical residue method for crops.

A Competitor Product Interference Study for the Analytical Residue Method for Tebuconazole and HWG 2061 Residues in Animal Tissues, Milk and Eggs;Report No. 101950; By R.R. Gronberg; October 14, 1991; MRID No. 422095-13.

As of September, 1991, 114 nitrogen and or phosphorous containing compounds had a registered tolerance in bovine and poultry meat, fat and by-products, milk and milk fat, or eggs as listed in "The Pesticide Chemical News Guide". These compounds were tested using the analytical residue method for animal tissues, milk, and eggs (Mobay Report No. 101316) and none of the compounds showed the potential to interfere with the analysis of tebuconazole and HWG 2061 residues.

**CBTS's Comments/Conclusions re: Deficiency No. 9**

The above submitted studies indicate that interference with the revised analytical methods with appropriate confirmatory procedures for detection of tebuconazole and its t-butylhydroxy metabolite is unlikely.

This deficiency is tentatively resolved.

**Deficiency No. 10**

Additional multiresidue testing data are required.

**Petitioner's Response to Deficiency No. 10**

The petitioner has submitted the following report:

Analysis of t-butylhydroxy Folicur (HWG 2061) According to Protocol B of PAM I, Multiresidue Screening; 2/22/92; MRID # 422095-09

The report describes the behavior of t-butylhydroxy Folicur (HWG 2061) when analyzed by Protocol B of Pam I, Multiresidue Screening. The report also provides the results for the analysis of t-butylhydroxy Folicur (HWG 2061) at various conditions, specified in Protocol C of Pam I.

The t-butylhydroxy Folicur (HWG 2061) does not give any gas chromatographic response at the concentration of 100 ng/ul, using the combination of columns and/or detectors listed in the PAM procedures. The methylated product of HWG 2061 also showed no gas chromatographic response except on a @% DEGs packed column using a Hall detector (Nitrogen mode), which gave a 50% FSD

response at the 40 ng/ul concentration; however the relative retention time was greator than 5 minutes. Based on these results, no additional testing was conducted.

The report also responded to the EPA question concerning clarification of the results of the Florisil column evaluation for multiresidue testing of tebuconazole and if adequate recoveries are possible a repeat of Protocol D and E method validations as follows:

> "There is a reported discrepancy in the recovery of tebuconazole from the Florisil columns. The data show good recovery from 10 ug/ml but not for 100ug. The reasons contributing to this disparity are as follows:
>
> a. The final volume for GC analysis was 5 ml with resulting concentrations (representing 100% recovery) of 2 ug/ml and 20 ug/ml respectively for 10 ug/ml and 100 ug/ml eluated from the Florisil column. The linearity curve shows linearity with the lowest concentration data point being 5.11 ug/ml which is 2.5 times the concentration required for the lowest level column recovery. Therefore, the data for the 10 ug column are below the GC detection limit, as defined by the lowest data point for the linearity curve. The linearity curve indicates that the 100 ug recovery data are more reliable.
>
> b. The cumulative recovery for the petroleum ether and ethyl ether/petroleum ether eluents from the 10 ug column is 160%. These data alone indicate that the recovery value for the 10 ug Florisil column are unreliable

**CBTS's Comments/Conclusions re: Deficiency No. 10**

Copies of the results of the subject multiresidue testing will be forwarded to the appropriate FDA and EPA officials.

This deficiency is tentatively resolved.

**Deficiency No. 11**

Storage stability data for processed plant products, additional referenced RAC data, and data for milk and eggs are required.

**Petitioner's Response to Deficiency No. 11**

The following is a summary of the storage stability data submitted:

Tebuconazole - A Poultry Feeding Study, MRID No. 422095-17

As discussed under Deficiency No. 16 storage stability data for poultry tissues and eggs after 23 weeks of storage at -24 C indicated that tebuconazole and the HWG 2061 metabolite were stable for the sample storage intervals between 124 to 179 days before sample analysis for the poultry feeding study. In summary after 23 weeks storage at -24 C the stability of C14 tebuconazole and HWG 2061 ranged from 94 to 100% and 97 to 100%, respectively for eggs, fat, skin, liver, and muscle using TLC and radiometric analysis.

Tebuconazole - A 28 Day Dairy Cattle Feeding Study, MRID No. 422095-18

As discussed under Deficiency No. 16 storage stability data for bovine liver, kidney, muscle, fat, and milk after 169 days of storage at -24 C indicated that tebuconazole and the HWG 2061 metabolite were stable for the sample storage intervals between 138 to 209 days before sample analysis for the cattle feeding study. In summary after 169 days storage at -24 C the stability of (triazole-UL-C14) tebuconazole and HWG 2061 ranged from 97.4 to 122.1% and 99.3 to 111.8%, respectively for bovine liver, kidney, muscle, fat, and milk using TLC and radiometric analysis. For the radiometric analysis the greatest percent probable error was calculated to be 5.5%.

Storage Stability of Tebuconazole in Dry Grape Pomace, Grape Juice Raisin Wastes, Peanut Meal, and Soapstock MRID No. 422095-15

In summary after six months storage at -24 C the degradation of (triazole-UL-C14) tebuconazole was 0, 1, <1, 3 and 3%, respectively for dry grape pomace, grape juice, raisin wastes, peanut meal and soapstock using TLC and radiometric analysis. Accordingly it was concluded that tebuconazole was stable in dry grape pomace, grape juice, raisin waste, peanut meal, and soapstock when stored under freezer conditions for six months.

Freezer Storage Stability of (14C) HWG 2061 in Peanut Hull, Foliage, and Meat and Grapes; MRID No. 422095-16

In summary after twelve months storage at -24 C the degradation of (triazole-UL-C14) HWG 2061 was 0, 0, 10, and 0%, respectively for peanut hulls, foliage, nutmeat, and grapes using TLC and radiometric analysis. Accordingly it was concluded that the metabolite HWG 2061 was stable in peanut hulls, foliage, nutmeat and grapes when stored under freezer conditions for 12 months.

Tebuconazole Freezer Storage Stability Study in Peaches, Prunes, Grapes, Apples, Cherries, Wheat Forage, Wheat Grain, Wheat Straw, and Peanut Nutmeat; MRID No. 422095-14

The analytical methodology used for the study was the Method in Mobay Report No. 94295 with the modifications described in Mobay Report No. 98520 (see Deficiency No. 7). The following

were the method recoveries obtained at fortification levels of 0.50 and 1.0 ppm tebuconazole.

| MATRIX | RECOVERY RANGE, % |
|---|---|
| Peaches | 86-91 |
| Prunes | 96-102 |
| Grapes | 87-88 |
| Apples | 93-95 |
| Cherries | 88-94 |
| Wheat Forage | 106-111 |
| Wheat Grain | 81-83 |
| Wheat Straw | 95-97 |
| Peanut Nutmeat | 83-91 |

The following table summarizes the storage stability of tebuconazole in the various matrices when stored frozen at -20 C for from 18 to 24 months:

| CROP MATRIX | LONGEST STORAGE INTERVAL (MONTHS) | AVERAGE STABILITY (%) TEBUCONAZOLE |
|---|---|---|
| PEACHES | 24 | 107 |
| PRUNES | 24 | 94 |
| GRAPES | 24 | 103 |
| APPLES | 24 | 93 |
| CHERRIES | 24 | 100 |
| WHEAT FORAGE | 18 | 88 |
| WHEAT GRAIN | 18 | 96 |
| WHEAT STRAW | 18 | 94 |
| PEANUT NUTMEAT | 18 | 109 |

**CBTS's Comments/Conclusions re: Deficiency No. 11**

The above storage stability data indicate that tebuconazole and its t-butylhydroxy metabolite (HWG 2061) are stable in animal commodities after six months of frozen storage. Although CBTS notes that some of the animal commodity samples in the feeding studies were stored frozen longer than six months (i.e up to 209 days) the above storage stability data indicates little if any degradation in animal matrices after six months of frozen storage and therefore adequately supports the longest frozen storage interval (i.e. 209 days) used in the cattle feeding study.

The above storage stability data indicate that tebuconazole is stable when stored frozen up to 24 months in fruit, up to 18

months in peanuts and wheat grain, forage and straw, up to 12 months in peanut hulls and foliage, up to 6 months in dry grape pomace, grape juice, raisin waste, peanut meal, and soapstock. CBTS notes that two of the peanut field trial studies included in this submission included a maximum frozen storage sample period of from 171 to 183 days and the third field trial study included a maximum frozen storage interval of up to 395 days. Although storage stability data for peanut hulls and foliage beyond 12 months was not submitted, the entire storage stability data provided (e.g. wheat and fruit) adequately support the third peanut field trial study. Processed peanut products were held in frozen storage up to a maximum of 135 and 331 days,in the second and third peanut processing studies, respectively while storage stability data is only available on peanut meal and soapstock up to six months.

For purposes of this petition adequate storage stability data are available to support the peanut field trial and animal feeding studies' data. However, additional storage stability data on peanut oil is required to support the peanut processing data.

This deficiency in not fully resolved.

**Deficiency No. 12 and 13**

12. Additional field trials for peanuts including the hydroxy metabolite will likely be needed.

13. Additional experimental data to support the seed grass, wheat, barley grape, and peanut field trials are required.

**Petitioner's Response to Deficiency No. 12 and 13**

1. Tebuconazole - Magnitude of the Residue on Peanuts, 3.6F
B. Williams, May 22, 1989, MRID No. 422095-20

Six residue studies were conducted on peanuts using seven ground applications of Tebuconazole 3.6F formulation at the application rate of 3.6 ounces a.i./A/application. The six residue studies were conducted in Texas, Oklahoma, North Carolina, Alabama, Mississippi, and Georgia which according to the USDA Publication, Agricultural Statistics - 1988, directly cover 86% of the U.S. peanut production area. Applications were made with ground equipment using spray volumes ranging from 9.8 to 24.94 gallons/A with the intervals between applications of 9 to 17 days.

Residue data were generated using the analytical procedure described in Mobay Report No. 94295 and modifications listed in Mobay Report No. 98530 (see Deficiency No. 10) at Analytical Bio- Chemistry Laboratories in Columbia, Missouri. Method validation recovery values in nutmeats at the 0.01, 0.02, 0.05, and 2.0 ppm levels ranged from 76-102% and recovery values in

vines at the 0.50, 1.0, 2.0 and 5.0 ppm levels ranged from 77-99%. Concurrent recoveries performed with this residue study ranged from 90-110% at the 0.01 ppm level in nutmeats, from 92-105% at the 1.0 ppm level in shells, and from 98-102% at the 20 ppm level in vines. Control values for peanut nutmeats, shells and vines ranged from <0.01, 0.02-0.08, 0.01-0.17 ppm, respectively. Treated peanut fraction samples were held frozen for a maximum of 183, 176 and 168 days for nutmeat, shells and vines, respectively. Copies of sample chromatagrams were provided

The tebuconazole residue data is summarized as follows:

| GROSS TEBUCONAZOLE RESIDUE (PPM) IN PEANUTS | | | | |
|---|---|---|---|---|
| LOCATION | PHI (DAYS) | NUTMEAT | SHELLS | VINES |
| TEXAS | 5 | 0.02 | 0.38 | 10.56 |
| | 14 | <0.01 | 0.17 | 12.54 |
| OKLAHOMA | 7 | 0.04 | 0.75 | 28.75 |
| | 14 | 0.08 | 1.82 | 16.99 |
| NORTH CAROLINA | 6 | 0.01 | 0.24 | 7.41 |
| | 13 | 0.01 | 0.31 | 6.78 |
| ALABAMA | 7 | <0.01 | 0.18 | 2.52 |
| | 14 | <0.01 | 0.27 | 1.76 |
| MISSISSIPPI | S7 | 0.05 | 2.02 | 8.44 |
| | 14 | 0.03 | 2.15 | 5.05 |
| GEORGIA | 3 | 0.02 | 0.54 | 14.35 |
| | 7 | 0.01 | 0.71 | 20.54 |

The petitioner concluded that the maximum gross tebuconazole residues found in peanut nutmeats, shells and vines (hay) was 0.08, 2.15 and 16.99 ppm, respectively, for the 14 day PHI.

2. Tebuconazole - Magnitude of the Residue on Peanuts, 3.6F
B. Williams, April 17,1990
MRID No. 422095-21

A total of four residue studies were conducted on peanuts, consisting of one using seven ground applications and three using seven aerial applications of Tebuconazole 3.6F formulation at the application rate of 3.6 ounces a.i./A/application. The four residue studies were conducted in Florida, Georgia, Oklahoma and Texas which according to the USDA Publication, Agricultural Statistics - 1989, directly cover 67% of the U.S. peanut production area. Applications were made with ground or aerial equipment using spray volumes ranging from 4.0

to 21.3 gallons/A with the intervals between applications of 13 to 18 days.

Residue data were generated using the analytical procedure described in Mobay Report No. 94295 and modifications listed in Mobay Report No. 98530 (see Deficiency No. 10) at Analytical Bio- Chemistry Laboratories in Columbia, Missouri. Method validation recovery values in nutmeats at the 0.01, 0.02, 0.05, and 2.0 ppm levels ranged from 76-102% and recovery values in vines at the 0.50, 1.0, 2.0 and 5.0 ppm levels ranged from 77-99%. Concurrent recoveries at the 0.10 ppm level were 79 and 94% in peanut hutmeats, 85 and 111% in shells and 76% in hay. Control values for peanut nutmeats, shells and vines ranged from <0.01 to 0.02, 0.01-0.30, 0.01-3.01 ppm, respectively with the higher values attributed to field contamination. Treated peanut fraction samples were held frozen for a maximum of 161, 164 and 171 days for nutmeat, shells and vines, respectively. Copies of sample chromatagrams were provided.

The tebuconazole residue data is summarized as follows:

| GROSS TEBUCONAZOLE RESIDUE IN PEANUTS (PPM) | | | | |
|---|---|---|---|---|
| LOCATION | PHI (DAYS) | NUTMEAT | SHELLS | HAY |
| GROUND APPLICATION | | | | |
| FLORIDA | 7 | 0.05 | 0.56 | 7.87 |
| | 14 | 0.03 | 0.37 | 5.14 |
| AERIAL APPLICATION | | | | |
| TEXAS | 6 | 0.04 | 0.54 | 2.43 |
| | 13 | 0.03 | 0.49 | 18.32 |
| OKLAHOMA | 7 | <0.01 | 0.02 | 10.86 |
| | 14 | <0.01 | 0.14 | 3.73 |
| GEORGIA | 7 | 0.01 | 0.46 | 13.54 |
| | 14 | <0.01 | 0.45 | 11.29 |

The petitioner concluded that the maximum gross tebuconazole residues found in peanut nutmeats, shells and vines (hay) was 0.03, 0.49 and 18.32 ppm, respectively, for the 14 day PHI.

3. Tebuconazole - Magnitude of the Residue on Peanuts, 3.6F
K. Pitcher , November 22, 1991
MRID No. 422095-22

A total of four residue studies were conducted on peanuts, consisting of a total of 7 ground applications at 14 day intervals of the Tebuconazole 3.6F formulation at the application rate of 3.6 ounces a.i./A/application; except in the residue

study in Georgia, the first two of seven applications were made at 1/5 the desired rate or 0.72 ounces a.i./A/application. Since the current proposed label disallows applications 1, 2 and 7, the residue data still reflect an exaggerated application rate (i.e. The proposed label for Folicur 3.6F provides for a total of 4 applications made as applications 3, 4, 5 and 6 in a normal 7-application season-long schedule). The four residue studies were conducted in Oklahoma, North Carolina, Georgia and Florida which based on to the USDA Publication, Agricultural Statistics - 1989, directly cover 58% of the U.S. peanut production area. Applications were made with ground or aerial equipment using spray volumes ranging from 4.0 to 21.3 gallons/A with the intervals between applications of 13 to 18 days.

Residue data were generated using the analytical procedure described in Mobay Report No. 101341 which is a revision of Mobay method 94295 and includes all matrix specific modifications that were used in the peanut processing study (see Deficiency No. 10) at Mobay Corporation, Agricultural Chemicals Division, Residue Analysis Laboratory at Kansas City, Missouri. Method validation recovery values in nutmeats at the 0.05 and .20 ppm levels ranged from 88-122%, and recovery levels in shells at 0.10, 0.50 and 3.00 ppm ranged from 73-124% and recovery values in hay at the 0.50, 5.0, 30 and 40 ppm levels ranged from 70-98%. Control values for peanut nutmeats, shells and vines ranged from <0.05, <0.10-0.10, <0.01 ppm, respectively. Treated peanut fraction samples were held frozen for a maximum of 341, 395 and 383 days for nutmeat, shells and vines, respectively. No significant decline in tebuconazole residues would be expected based on available storage stability data. Copies of sample chromatagrams were provided.

The tebuconazole residue data are summarized as follows:

| GROSS TEBUCONAZOLE RESIDUE (PPM) IN PEANUTS | | | | |
|---|---|---|---|---|
| LOCATION | PHI (DAYS) | NUTMEAT | SHELLS | HAY |
| OKLAHOMA | 7 | <0.05 | 1.80 | 22.27 |
| | 14 | <0.05 | 1.16 | 9.07 |
| NORTH CAROLINA | 7 | 0.05 | 0.50 | 17.95 |
| | 14 | <0.05 | 0.55 | 15.45 |
| GEORGIA | 7 | <0.05 | 0.28 | 13.43 |
| | 14 | <0.05 | 0.46 | 8.57 |
| FLORIDA | 7 | 0.05 | 0.79 | 13.89 |
| | 14 | <0.05 | 0.85 | 9.38 |

**CBTS Comments/Conclusions re: Deficiency No. 12 and 13**

The maximum tebuconazole residues detected in the peanut field trials for a 13 to 14 day PHI was 0.08, 2.15 and 18.32 ppm in peanut nutmeat, shells and hay, respectively. However, the petitioner uses the terms "vines" and "hay" in their field trial reports. Do they refer to the same commodity? Miles Inc. should clarify exactly how these samples were obtained and provide some indication of their moisture content. A revised Section B and/or F may be needed depending on the nature of the samples that were analyzed. , CBTS tentatively concludes that the new peanut field trial data summarized above supports the proposed permanent tolerances for tebuconazole in/on peanut nutmeat, shells and hay/vines of 0.1, 4 and 25 ppm, respectively based on the current proposed use of up to four applications of Folicur 3.6 F (at a rate of 8 fluid ounces/A at 3.6 lbs a.i./gallon or 3.6 ounces a.i./A) at 14 day intervals and a 14 day PHI, with a maximum seasonal application of 1 quart or 32 fluid ounce of Folicur 3.6 F (0.9 lb a.i./A). Folicur 3.6F may be applied in a minimum of 10 gallons of spray solution per acre by ground sprayer or in aminimum of 5 gallons of spray solution by aircraft application. CBTS notes that the petitioner has included on the label, recommendations to use an alternate fungicide (i.e. Non-Sterol Inhibitor Fungicide) for either applications 1 and 6 or 1, 2, and 7 of the total 7 applications recommended for adequate disease control.

Additional data to support the proposed uses of tebuconazole on seed grass, wheat, barley, and grapes are tentatively not required since proposed permanent tolerances on these crops have been withdrawn. In light of the new peanut field trial data additional experimental data on the previous peanut field trial data is not required. Per a December 6, 1991 memo of R. Quick and E. Zager - Requirement For Crop Field Trials to Support Aerial Applications crop field trials reflecting aerial application are no longer required provided adequate residue data are available from the use of ground equipment and aerial application are to be made in a minimum of 2 gallons water per acre. Also CBTS notes that the petitioner has provided three peanut field trials using aerial application and tebuconazole residue levels were comparable to that obtained from the ground application field trials.

These deficiencies are tentatively resolved, pending resolution of Deficiency No. 6 (i.e. vines/hay).

**Deficiency Nos. 14 and 15**

14. Additional data on the wheat processing study and residue data on grain dust are required.

15. Additional data on the grape processing study are required.

**Petitioner's Response to Deficiency Nos. 14 and 15**

The petitioner has withdrawn proposed permanent tolerances on wheat and grapes.

**CBTS's Comments/Conclusions re: Deficiency Nos. 14 and 15**

Since proposed permanent tolerances on wheat and grapes have been withdrawn, these deficiencies are no longer applicable to the current proposed use on peanuts.

These deficiencies are tentatively resolved.

**Deficiency No. 16 and 19**

Additional experimental data on the poultry and ruminant feeding studies are required.

**Petitioner's Response to Deficiency No. 16 and 19**

The petitioner has submitted new dairy cattle and poultry feeding studies.

Tebuconazole - A 28-Day Dairy Cattle Feeding Study
H.M. Chopade and T.L. Fitzpatrick, October 15, 1991
MRID NO. 422095-18

A tebuconazole dairy cattle feeding study was conducted in 1988. Due to deficiencies in the analytical data, the lack of concurrent storage stability data in tissues and milk, and a question of the adequacy of the 1X (25 ppm) treatment level, the petitioner conducted a new dairy cattle feeding study.

Ten Holstein Fresian dairy cattle (three cows per treatment group and one cow as a control) were fed daily with capsules containing technical tebuconazole (95.2% a.i.) at levels equivalent to 0, 30, 90 and 300 ppm (i.e. 1, 3, and 10X based on the original proposed uses) in the feed for a period of 28 days at the facilities of Mobay Research Park located near Stilwell, Kansas.

Sample dosage calculations were provided. Dosage capsules were stored in a refrigerator except a one-week supply of capsules for each treatment group was removed from cold storage and kept at room temperature in the dairy facility. Duplicate capsules from each dosage group were randomly sampled to verify the amount of tebuconazole in them. A concurrent storage stability study of tebuconazole and HWG 2061 in the tissues and milk was also conducted for the duration of the study. The stability of tebuconazole on the alpha-lactose in the gelatin capsules, refrigerated milk, and frozen tissues and milk was verified with (triazole-UL-14C) tebuconazole and quantitation by TLC and radiometric analysis.

The dosage capsules were administered orally once per day after morning milking using a metallic balling gun. The cows were milked morning and evening with the milk samples immediately transferred to a walk-in refrigerator with aliquots of the evening milk and the following morning's milk mixed together to form a sample representative of a single day. On the 28th day, the dosage capsules were administered to the cows after the evening milking at 6 p.m. and the next morning, the animals were weighed and milked with sacrifice within 16 hours following the last dose. At the time of sacrifice, between 1 and 2 kg each of liver, kidney, muscle (composite of flank, loin and round), and fat (composite of renal, omental and subcutaneous) were taken from each animal for residue analysis. Upon collection, the tissues were immediately cut into small pieces and kept in a walk-in freezer overnight. The frozen, chopped pieces of individual tissues were pulverized with dry ice nuggets in a Hobart Food Cutter. The processed tissues were stored in a walk-in freezer until the dry ice sublimed.

The number of days from sample collection to analysis ranged from 154 to 209 days. The concurrent storage stability study showed complete stability of tebuconazole and HWG 2061 in bovine liver, kidney, muscle, fat, and milk stored frozen at -24 C for up to 169 days. Aliquots (40 g) of the tissue and milk samples were analyzed for tebuconazole and HWG 2061 residues using the method of Gronberg et al. (See Deficiency No. 8) and copies of sample chromatagrams were provided. The average recoveries of tebuconazole and HWG 2061 in milk were 88 and 84%, respectively and in tissue 96 and 92%, respectively. The limit of determination for the analytical methodology was 0.05 ppm for milk and 0.1 ppm for tissues.

The following tables summarize the tissue and 28 day milk residue data uncorrected for average method recoveries, obtained for each cow in the study. The term NA means that the sample was not analyzed due to the absence of a detectable residue at the higher feeding level:

| PPM of Tebuconazole | | | | | |
|---|---|---|---|---|---|
| PPM/DOSE | LIVER | KIDNEY | MUSCLE | FAT | MILK |
| CONTROL | <0.1 | <0.1 | <0.1 | <0.1 | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 90 | 0.2 | <0.1 | NA | NA | <0.05 |
| 90 | 0.1 | <0.1 | NA | NA | <0.05 |
| 90 | 0.2 | <0.1 | NA | NA | <0.05 |
| 300 | 0.4 | <0.1 | <0.1 | <0.1 | <0.05 |
| 300 | 0.8 | <0.1 | <0.1 | <0.1 | <0.05 |
| 300 | 0.7 | <0.1 | <0.1 | <0.1 | <0.05 |

| PPM of HWG 2061 Metabolite | | | | | |
|---|---|---|---|---|---|
| PPM/DOSE | LIVER | KIDNEY | MUSCLE | FAT | MILK |
| CONTROL | <0.1 | <0.1 | <0.1 | <0.1 | <0.05 |
| 30 | 0.1 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 90 | 0.6 | 0.7 | NA | NA | <0.05 |
| 90 | 0.4 | 0.9 | NA | NA | <0.05 |
| 90 | 0.6 | 0.6 | NA | NA | <0.05 |
| 300 | 1.9 | 1.2 | <0.1 | <0.1 | 0.06 |
| 300 | 1.5 | 2.2 | <0.1 | <0.1 | 0.10 |
| 300 | 1.3 | 1.5 | <0.1 | <0.1 | 0.12 |

| Total PPM of Tebuconazole and HWG 2061 | | | | | |
|---|---|---|---|---|---|
| PPM/DOSE | LIVER | KIDNEY | MUSCLE | FAT | MILK |
| CONTROL | <0.1 | <0.1 | <0.1 | <0.1 | <0.05 |
| 30 | 0.2 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 30 | <0.1 | <0.1 | NA | NA | <0.05 |
| 90 | 0.8 | 0.6 | NA | NA | <0.05 |
| 90 | 0.4 | 0.9 | NA | NA | <0.05 |
| 90 | 0.8 | 0.6 | NA | NA | <0.05 |
| 300 | 2.2 | 1.2 | <0.1 | <0.1 | 0.06 |
| 300 | 2.3 | 2.2 | <0.1 | 0.2 | 0.10 |
| 300 | 1.9 | 1.5 | <0.1 | <0.1 | 0.12 |

The petitioner concluded that liver contained the highest residues levels of tebuconazole with 0.8 ppm in the 300 ppm dose group, 0.2 ppm in the 90 ppm dose group and <0.1 ppm in the 30 ppm dose group. The residue of HWG 2061 in tissues was higher than the tebuconazole residue. The highest HWG 2061 residue levels were 2.2 ppm in liver and 1.9 ppm in kidney, from the 300 ppm dosage group. The HWG 2061 residue levels from the 90 ppm dosage group in liver and kidney were 0.6 and 0.9 ppm, respectively, and from the 30 ppm dosage group 0.1 ppm in the liver. Fat and muscle from the 300 ppm dosage group contained <0.1 to 0.1 ppm tebuconazole and HWG 2061. The tebuconazole residue in the milk samples from all the dosage groups was <0.05 ppm. The residue of HWG 2061 in the milk from the 300 ppm dosage group reached 1.2 ppm by the end of the 28-day study and residues in milk from the 30 and 90 ppm dosage groups was <0.05 ppm. Residue data was also presented on Day 7, 14, and 21 milk but detectable residues of HWG 2061 were found only in the 300 ppm dosage group and all at lower levels than the 28 Day milk (e.g. <0.05, 0.06 and 0.09 ppm in the Day 14 milk).

Tebuconazole - A 28-Day Poultry Feeding Study
A. Mathew, C. Blum and D. Unruh: October 15, 1991
MRID No. 422095-17

Although a previous poultry feeding study with tebuconazole has been submitted, due to shortcomings in the analytical data, the lack of concurrent storage stability data, and other deficiencies, the decision was made to conduct a new poultry feeding study with tebuconazole.

Forty-eight healthy and good White Leghorn egg laying hens were weighed and divided into four dosage groups (0, 2, 6, and 20 ppm representing 1X, 3X and 10X) of 12 hens each, with each group of birds further subdivided into three subgroups of four hens each. Hens were given fortified feed for 28 days at Mobay Research Park near Stilwell, Kansas. Poultry feed was fortified with a solution of tebuconazole in corn oil prepared by dissolving the appropriate amount of tebuconazole in 50 ml acetone and then mixing the acetone solution with 160 g of corn oil at levels of 2, 6 and 20 Control feed contained only corn oil (160 g) and acetone (50 ml).

Feed was stored in a refrigerator (6 C) until used in the study. Analysis of 20 ppm feed stored in the refrigerator for 65 days indicated that tebuconazole in the stored feed was stable during the entire feeding study. Although 150 g of feed were provided every day for each bird, the feed which was not eaten each day was left to accumulate in the tray (no longer than 1 week). Analysis of 20 ppm feed left at room temperature for nearly 2 weeks indicated that tebuconazole would be stable in the feed when left in the tray for one week.

Sample calculations for calculating the level of tebuconazole (ppm) in the chicken feed were provided. The mean concentrations of tebuconazole in the chicken feed fortified where extractions were done immediately after feed preparation were 0.42, 2.20, 7.18, and 22.52 ppm for the control 2 6 and 20 ppm dosage groups, respectively while the levels in the 20 ppm fortified feed stored at room temperature for 12 days and in the refrigerator for 65 days were 22.87 and 22.75 ppm, respectively. A concurrent storage stability study on liver, muscle, fat, skin and egg samples was also conducted with (triazole-UL-14C) tebuconazole and quantitation by TLC and radiometric analysis. Both tebuconazole and HWG 2061 were found to be stable (percent degradation for egg, fat, skin, liver, and muscle of 0, 0, 0, 1 and 5%, and 7, 0, 1, 0 and 1%, respectively for tebuconazole and HWG 2061) when stored frozen (-24 C) after 23 weeks.

Every day, the eggs produced by each four-hen subgroup were cracked, and the contents separated from the shells, mixed thoroughly, weighed and frozen. After 28 days of feeding the hens were weighed and sacrificed. Liver, composite muscle (breast, leg and thigh) and composite fat (omental, subcutaneous and renal) samples were placed in labeled plastic bags, and stored in a freezer (-24 C) prior to, processing the next day. For each four hen subgroup, the frozen tissues were pulverized with dry ice using a food cutter. The samples were stored in the freezer (-24) for later analysis.

Aliquots (40 g) of the tissue and egg samples were analyzed for tebuconazole and HWG 2061 using the analytical method of Gronberg, et al. (see Deficiency No. 8) and copies of sample chromatograms were provided. For residue analysis, a set of five samples of 40 g each were used. There were three replicates per treatment group (subgroups A, B, and C), a control sample and a

control sample fortified with tebuconazole and HWG 2061 each at 0.1 ppm. Tissue and egg extracts were stored in a refrigerator (1 C) for less than a week until analyzed. Average recoveries in poultry tissue and eggs for tebuconazole and HWG 2061 were 91 ±14% and 79 ±8%. The limit of determination for the analytical methodology was 0.1 ppm for both tissue and eggs.

The following tables summarize the poultry tissue and 28 day egg residue data uncorrected for average method recoveries. The term NA means that the sample was not analyzed due to the absence of a detectable residue at the higher feeding level:

| RESIDUES OF TEBUCONAZOLE (PPM) | | | | |
|---|---|---|---|---|
| TISSUE | 0 PPM DOSE | 2 PPM DOSE | 6 PPM DOSE | 20 PPM DOSE |
| LIVER | <0.1 | NA | <0.1 | <0.1 |
| MUSCLE | <0.1 | NA | NA | <0.1 |
| FAT | <0.1 | NA | NA | <0.1 |
| SKIN | <0.1 | NA | NA | <0.1 |
| EGG | <0.1 | NA | NA | <0.1 |

| RESIDUES OF HWG 2061 (PPM) | | | | |
|---|---|---|---|---|
| TISSUE | 0 PPM DOSE | 2 PPM DOSE | 6 PPM DOSE | 20 PPM DOSE |
| LIVER | <0.1 | NA | <0.1 | 0.2 |
| MUSCLE | <0.1 | NA | NA | <0.1 |
| FAT | <0.1 | NA | NA | <0.1 |
| SKIN | <0.1 | NA | NA | <0.1 |
| EGG | <0.1 | NA | NA | <0.1 |

| TOTAL RESIDUES OF TEBUCONAZOLE AND HWG 2061 (PPM) | | | | |
|---|---|---|---|---|
| TISSUE | 0 PPM DOSE | 2 PPM DOSE | 6 PPM DOSE | 20 PPM DOSE |
| LIVER | <0.1 | NA | <0.1 | 0.2 |
| MUSCLE | <0.1 | NA | NA | <0.1 |
| FAT | <0.1 | NA | NA | <0.1 |
| SKIN | <0.1 | NA | NA | <0.1 |
| EGG | <0.1 | NA | NA | <0.1 |

The petitioner concluded that residues in poultry muscle, skin, fat and egg (including 7, 14, 21 and 28 day eggs) were <0.1 ppm for both tebuconazole and HWG 2061 in the highest (20 ppm) dose group. The total residue (tebuconazole and HWG 2061) in tebuconazole equivalents in liver from the 20 ppm dose group was

0.2 ppm, almost all of which was found to be HWG 2061 and from the 6 ppm dose group was <0.1 ppm. Since the other tissues and eggs in the highest dose group contained <0.1 ppm total tebuconazole residues, the 6 and 2 ppm dose groups were not analyzed.

**CBTS's Comments/Conclusions re: Deficiency No. 16 and 19**

The new ruminant and poultry feeding studies are acceptable and support the proposed tolerances for tebuconazole and HWG 2061 of 0.05 ppm for milk and 0.1 ppm for eggs and meat, fat, and meat byproducts of poultry, cattle, goats, hogs, horses, and sheep.

These deficiencies are resolved.

**Deficiency No. 17**

Additional data on the peanut processing study are required. A new peanut processing study will be needed if the hydroxy metabolite is added to the tolerance expression.

**Petitioner's Response to Deficiency No. 17**

The petitioner has submitted a third peanut processing study:

Tebuconazole (3.6F) - Magnitude of the Residue on Peanut Processed Products; October 24, 1991; MRID # 422095-23

In summary Seven foliar spray applications of Folicur 3.6F were applied to peanut plants at approximate 14-16 day treatment intervals with two applications using ground equipment at a rate of 3.6 oz a.i./A per application and five applications at a rate of 18 oz a.i./A per application (total 97.2 oz) which represents approximately 3.4X the maximum proposed application rate. Samples of mature nuts were dug 7 days following the last application and allowed to field dry for 11 days prior to harvesting and subsequent processing. After harvest mature nuts in shells were stored two days at ambient temperature (73 F) before they were shipped unfrozen the next day to the processing facility and remained at room temperature for approximately 9 days before sample processing into presscake and crude oil which were immediately placed into frozen storage and removed in five days for further processing into soapstock and refined oil.

The peanut processing was done by Texas A&M University and the procedures included drying and cleaning, hulling and separation, conditioning and pressing, solvent extraction (with hexane at (120-140 F), crude oil recovery and oil refining. The study indicates that a majority of the crude oil was released from the expeller with the residual oil left in the presscake extracted with solvent. All processed fractions were transferred to frozen storage at -20 C pending residue analysis at Mobay Research Park. Processed peanut samples were held in frozen

storage for a maximum of 331 days and the petitioner referenced storage stability data (see Deficiency No. 11) which indicated that tebuconazole was stable when stored frozen in peanuts for 1 year and in peanut meal and soapstock for 6 the month storage interval tested with a maximum degradation of 3%.

Residue data were obtained using the analytical procedure described in Mobay Report No. 101341 (see Deficiency No. 7). Method validation included fortifications in nut meat at 0.05 to 0.20 ppm with recoveries from 97 to 118%, in refined oil at 0.40 ppm with 80% recovery, in crude oil at 0.05 to 0.30 ppm with recovery from 90 to 106%, in meal from 0.05 to 0.20 and recovery from 85 to 86%, and in soapstock at 0.20 to 1.00 and recovery from 111 to 116%. The following table summarizes the residue data obtained:

| Sample Matrix | Tebuconazole (ppm) | Concentration Factor |
|---|---|---|
| Nut Meat | 0.10 | |
| Refined Oil | 0.23 | 2.3 |
| Crude Oil | 0.28 | 2.8 |
| Meal | 0.18 | 1.8 |
| Soapstock | 0.77 | 7.7 |

Sample calculations and copies of chromagrams were also provided.

Based on the above results the petitioner has proposed FAT's for tebuconazole on refined oil, crude oil, meal at 0.5 ppm and on soapstock of 1.0 ppm based on a proposed tolerance level on peanuts of .10 ppm.

**CBTS's Comments/Conclusions re: Deficiency No. 17**

Of the two previously submitted peanut processing studies (see PP#9G3817 6/8/90 review of C. Olinger), in one study no residues were detected in any matrix except soapstock and in the other study tebuconazole residues in the nutmeat were 0.08 ppm with the resulting concentration factor from processing of 4.4 and 2.5 for crude oil from the expeller and solvent extraction, respectively, 3.3 for refined oil and 3.8 for soapstock with no FAT for solvent extraction meal required since the residue was 0.04 ppm.

CBTS notes the concentration of tebuconazole in both the peanut meal and oil in the new processing study without any explanation in the processing report and further that the residue samples were stored frozen up to 331 days before analysis while storage stability data for processed peanut products for this duration have not been submitted. Processed peanut products were held in frozen storage up to a maximum of 135 and 331 days, in the second and third peanut processing studies, respectively while storage stability data is only available on peanut meal and

soapstock up to six months. Additional storage stability data is required (particularly for peanut oil) to support the two processing studies (see Deficiency No. 11). The petitioner should respond collectively to the storage stability deficiencies of the two processing studies.

Also, the petitioner should confirm for the new processing study if crude oil from the expeller and solvent extraction of the presscake were combined before analysis and provide a comparison of the crude oil concentration factors of the two processing studies using a weighted average concentration of the crude oil (from the expeller and solvent extraction) with a discussion of any significant differences.

CBTS concludes that an explanation of the concentration of tebuconazole in both the meal and oil from the new study as well as a discussion of the storage stability of the peanut processed fractions in both processing studies in light of all the currently available storage stability data is required. At least some additional storage stability data on peanut oil is required. We note that the concentration factors for peanut oil from the second and third processing studies are similar but an explanation of the inconsistency in meal is needed. Establishing FAT's on both peanut meal and peanut oil is not acceptable. Any rationale for extrapolating storage stability data from different processed matrices or RAC's or from shorter time intervals must be supported by a reasonable rationale. A decision on the proposed FAT's and the two peanut processing studies considered collectively is deferred pending an appropriate response from the petitioner.

This deficiency is not resolved.

**Deficiency No. 20**

A Section F with revised RAC, processed product and meat, milk, poultry and egg tolerances is required.

**Petitioner's Response to Deficiency No. 20**

The petitioner has submitted a revised Section F with proposed tolerances for tebuconazole and HWG 2061 of 0.05 ppm for milk and 0.1 ppm for eggs and meat, fat, and meat byproducts of poultry, cattle, goats, hogs, horses, and sheep.

**CBTS's Comments/Conclusions re: Deficiency No. 20**

In accordance with CBTS's Conclusions on Deficiency No. 17 Proposed FAT's for both peanut oil and meal are not acceptable. Concentration in both fractions is not possible. Based on the required explanation of the conflicting results of the two processing studies, a revised Section F will be required.

This deficiency is not yet resolved (New Deficiency No. 6).

**Other Considerations**

An International Residue Limit Status Sheet is included in this review as **Attachment 3.** Since no Codex, Canadian, or Mexican limits/tolerances have been established for tebuconazole, there are no compatibility problems at this time.

Attachment 1 - Confidential Appendix
Attachment 2 - Peanut Metabolism Data
Attachment 3 - International Residue Limit Status Sheet

cc **With Attachment 1:** PP#9F3724

cc **Without Attachment 1:** Reviewer-Otakie, RF, Circu, PP#9G3817, E. Haeberer,
RDI: EHaeberer:2/8/93 RLoranger:2/9/93