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

OFFICE OF
PREVENTION, PESTICIDES,
AND TOXIC SUBSTANCES

**MEMORANDUM**

Date: November 2, 2005

Subject: Bitertanol. Summary of Analytical Chemistry and Residue Data for the Tolerance Reassessment Eligibility Decision (TRED) Document.

DP Barcode: D302882 PC Code: 117801
40 CFR §: 180.457 Chemical Class: Azole

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This summary of analytical chemistry and residue data document was originally prepared under contract by Versar, Inc. (6850 Versar Center, Springfield, VA 22151; submitted August 16, 2004). The summary document has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Program (OPP) policies.

**Executive Summary**

Bitertanol, β-([1,1 '-biphenyl]-4-yloxy)-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol, is a fungicide used for the control of black sigatoka, a fungal disease that destroys the leaf tissue of the banana plant. Bitertanol is formulated as an emulsifiable concentrate (EC) or suspension concentrate (SC) and may be applied as a foliar spray by airplane, tractor driven equipment, or knapsack sprayer. Bitertanol end-use products are marketed under the trade name Baycor®. The active ingredient constitutes 30% for the EC formulation and 50% for the SC formulation. Applications are as needed and based on the speed of leaf emergence with a maximum of 8 applications during the development period of a fruit bunch. The rate per application is 0.13 lb ai/A for a maximum seasonal application rate of 1.1 lb ai/A. It is intended for use on bagged bananas only. There are no U.S. registrations for bitertanol.

A tolerance has been established under 40 CFR §180.457 for the residues of bitertanol in/on bananas at 0.20 ppm. This tolerance is an import tolerance since bitertanol is not registered for use in the U.S. The Codex Alimentarius Commission (Codex) has established a maximum residue limit (MRL) for bitertanol residues in/on bananas at 0.5 mg/kg. Additionally, the Codex MRL for bitertanol is expressed in terms of residues of bitertanol only, as is the U.S. tolerance expression. It is the Agency's policy to harmonize its tolerances with the levels established by Codex provided that the Agency has sufficient information to make a determination that the Codex MRLs will be protective of the health of the U.S. public and meet FFDCA standards. The established tolerance should be reassessed to 0.50 ppm to harmonize with Codex as the dietary exposure and risk are not of concern (S. Ary, D302880, 11/2/2005).

The nature of residues in plants is adequately understood based on acceptable plant metabolism studies in apples and peanuts conducted with bitertanol labeled in the biphenyl ring system and additional studies submitted recently in apples, cotton, and tomatoes conducted with bitertanol labeled in the traizole ring system. The recently submitted studies are currently under review by the Agency, however it is noted that after initial review of the newly submitted studies, the data support the conclusions drawn from the two previous submissions. The residues identified in these studies consisted primarily of the parent compound with traces of the metabolites bitertanol ketone and 4-hydroxybiphenol. Although no metabolism studies for bananas are available, HED has concluded that the nature of residues in bananas is likely similar to that in apples, cotton, peanuts, and tomatoes. Therefore, HED has determined that the bitertanol residues of concern in/on bananas for tolerance expression and for risk assessment are bitertanol.

Additionally, the Agency does have concern about the potential toxicity of 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, which are metabolites common to most of the triazole fungicides. To support the extension of existing and granting of new parent triazole-derivative fungicide tolerances, the Agency will be conducting a human-health assessment for aggregate exposure to 1,2,4-triazole.

An analytical method for analysis of residues of bitertanol has been submitted and found acceptable for data collection purposes. The submitted method is a modification of Mobay Chemical Corporation's Method 54166 for the analysis of bitertanol in apples. Analysis is by gas chromatography using a nitrogen-phosphorus flame ionization detector. The limit of detection is

0.01 ppm. A method trial was successfully performed on banana pulp and peels at fortification levels of 0.1 ppm and 0.2 ppm. Recoveries ranged from 78 to 88% for pulp samples, and from 70 to 98% for peel samples. The method was approved by the Agency for the enforcement of tolerance in/on bananas and the results were forwarded to FDA for inclusion in the Pesticide Analytical Manual (PAM) Volume II.

The FDA PESTDATA database dated 11/2001 (PAM Volume I, Appendix I) indicates that bitertanol was completely recovered using Multiresidue Method Section 302 (Protocol D).

Storage stability data for bitertanol in/on bananas have not been submitted by the registrant, therefore, storage stability data are required

As indicated in the tolerance petition, bitertanol was originally marketed for use on bananas in Costa Rica and Honduras, but has expanded to include Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Peru, Venezuela, Dominican Republic, and Panama. Residue data from trials conducted in Costa Rica and Honduras have been submitted and reviewed by the Agency. Bitertanol was applied to both bagged and unbagged bunches of green and ripe bananas at a rate of 0.26 lb ai/A/application (2x the current rate per application), the maximum rate per application indicated on the product label at that time. Samples of peel, pulp and whole fruit were collected 3 days after the last of 9 treatments and 0 days after the last of 12 treatments. Washed and unwashed samples were analyzed for bitertanol by Method 54166, with modifications. The number of trials, the location of the trials within Costa Rica and Honduras, and the formulation type were not specified. No data were provided on how long the samples were stored prior to analysis. Residues found in samples of whole fruit from unbagged and bagged bunches of ripe and green bananas were all below the recommended tolerance level of 0.5 ppm. The residue data are deemed adequate to support a tolerance of 0.5 ppm in/on bananas.

The SC formulation will be supported with additional field trials that are currently being conducted by the registrant. The studies are planned for completion in 2006.

**Regulatory Recommendations and Residue Chemistry Deficiencies**

- Revise tolerance to 0.50 ppm to harmonize with Codex.
- Storage stability data are required to determine the stability of residues in bananas during cold storage. No data were provided on how long the banana samples from submitted field trial studies were stored prior to analysis.
- Field trial data for the SC formulation are required.
- Additional data are required in order for the submitted field trials conducted in Costa Rica and Honduras to be acceptable. The number of trials, location of the trials within the countries, and the formulation type used.

## Background

The chemical structure and nomenclature of bitertanol are listed in Table 1 and the chemical names and structures of the metabolites of bitertanol are presented in Table 3. Table 2 presents the physicochemical properties of bitertanol.

**Table 1. Test Compound Nomenclature.**

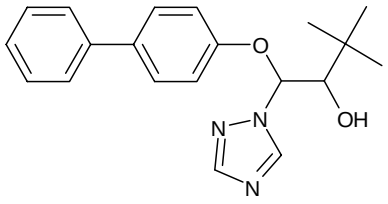
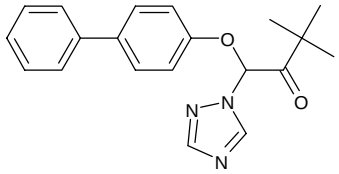
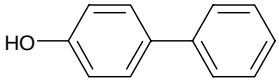
| | |
|---|---|
| Chemical structure |  |
| Common name | Bitertanol |
| Trade name | Baycor® |
| Company experimental name | KWG 0599 |
| Molecular formula | $C_{20}H_{23}N_3O_2$ |
| IUPAC name | 1-(biphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol |
| CAS name | β-(1,1'-biphenyl)-4-yloxy-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol |
| CAS number | 55179-31-2 |
| PC Code | 117801 |

**Table 2. Physicochemical Properties of the Technical Grade Test Compound.**

| Parameter | Value | Reference |
|---|---|---|
| Molecular weight | 337.42 g/mol | MRID 46655901 |
| Melting point/range | 145-155°C | MRID 46655901 |
| pH | Not available | |
| Density | 1.16 g/mL at 20°C | MRID 46655901 |
| Water solubility | 1.1 mg/L at 20°C for isomer A | MRID 46655901 |
| | 2.7 mg/L at 20°C for isomer B | |
| Solvent solubility (temperature not specified) | 1-5 g/100g of propan-2-ol,<br>1-5 g/100g of toluene,<br>5-10 g/100g of cyclohexane,<br>10-20 g/100g of methylene chloride<br>Stable in aqueous acid and alkaline solutions. | Merck Index 12th Edition |
| Vapor pressure | 10-5 mBar at 20°C | Merck Index 12th Edition |
| Dissociation constant ($pK_a$) | None | MRID 46655901 |
| Octanol/water partition coefficient Log($K_{OW}$) | $K_{ow}$ log P = 4.04 at 20°C for isomer A | MRID 46655901 |
| | $K_{ow}$ log P = 4.10 at 20°C for isomer B | |
| UV/visible absorption spectrum | Peak maximum at 255 nm | MRID 46655901 |

| Table 3. Chemical Names and Structures of Metabolites of Bitertanol. | | |
|---|---|---|
| Common Name | Chemical Name | Structure |
| bitertanol ketone | 1-[(1,1-biphenyl)-4-yloxy]-3,3-dimethyl-1-(1H-1,2,4-triazole-1-yl)-2-butanone |  |
| p-hydroxybiphenyl | 4-hydroxybiphenyl |  |

## Summary of Science Findings

## 860.1200 Directions for Use

## Product List

There are no U.S. registrations for bitertanol. An import tolerance for residues of bitertanol in/on bananas was established through a petition (PP# 2E2756) submitted by Mobay Chemical Corporation. As indicated in the tolerance petition, bitertanol was originally marketed for use on bananas in Costa Rica and Honduras, but has expanded to include Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Peru, Venezuela, Dominican Republic, and Panama. There are two Bayer CropScience end-use products containing the active ingredient bitertanol as indicated in Table 4. The variation in product names reflect different product naming requirements depending on which country each product is registered in.

| Table 4. Bitertanol End-Use Products (EPs) with Food/Feed Uses. | | | | | |
|---|---|---|---|---|---|
| EPA Reg. No.[1] | Formulation[2] | Label Acceptance Date[1] | Registrant | Product Name | Commodity |
| N/A = not applicable | 30% EC | N/A | Bayer CropScience | Baycor® 300 EC, Baycor® 30 EC, Baycor® 300 DC, and Baycor® 300 CE | Banana |
| N/A | 50% SC | N/A | Bayer CropScience | Baycor® 500 EC and Baycor® 50 SC | Banana |

1. There are no U.S. registrations for bitertanol.
2. EC = emulsifiable concentrate and SC = soluble concentrate.

Bitertanol is formulated as an emulsifiable concentrate (EC) or suspension concentrate (SC) and may be applied as a foliar spray by airplane, tractor driven equipment, or knapsack sprayer. The active ingredient constitutes 30% for the EC formulation and 50% for the SC formulation. Applications are as needed and based on the speed of leaf emergence with a maximum of 8 applications during the development period of a fruit bunch. The rate per application is 0.13 lb ai/A for a maximum seasonal application rate of 1.06 lb ai/A. It is intended for use on bagged bananas only, however, application to unbagged bananas may occur. The current labels do not

restrict application to bagged bananas and does not specify any pre-harvest interval (PHI) requirements.

There are no U.S. registrations for bitertanol. An import tolerance for residues of bitertanol in/on bananas was established through a petition (PP# 2E2756) submitted by Mobay Chemical Corporation. As indicated in the tolerance petition, bitertanol was originally marketed for use on bananas in Costa Rica and Honduras, but has expanded to include Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Peru, Venezuela, Dominican Republic, and Panama.

Bitertanol is formulated as an EC that contains 30% active ingredient (Baycor® 300 EC, Baycor® 30 EC, Baycor® 300 DC, and Baycor® 300CE) or SC that contains 50% active ingredient (Baycor® 500 EC and Baycor® 50SC).

**Use Patterns**

A summary of the direction for the use of bitertanol is presented in Table 5. Based on label information provided by the petitioner, bitertanol can be applied as needed based on the speed of leaf emergence with a maximum of 8 applications during the development period of a fruit bunch. The maximum rate per application is 0.133 lb ai/A for a total seasonal application rate of 1.064 lb ai/A. Bitertanol can be applied as a foliar spray by air in a minimum of 2 gallons of water per acre. It is intended for use on bagged bananas only, however, application to unbagged bananas may occur. The current labels do not restrict application to bagged bananas and does not specify any PHI requirements.

**Table 5. Summary of Directions for Use of Bitertanol.**

| Applic. Timing, Type, and Equip. | Formulation | Applic. Rate (lb ai/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ai/A) | PHI (days) |
|---|---|---|---|---|---|
| Banana | | | | | |
| Apply as needed based on speed of leaf emergence during fruit development. Minimum retreatment interval of 7 days. Apply specified dosage as a foliar spray by air, tractor driven equipment, or knapsack sprayer in a minimum of 2 gallons of water per acre. | Baycor® 30% EC | 0.13 lb ai/A | 8 | 1.06 lb ai/A | None |
| Apply as needed based on speed of leaf emergence during fruit development. Minimum retreatment interval of 7 days. Apply specified dosage as a foliar spray by air, tractor driven equipment, or knapsack sprayer in a minimum of 2 gallons of water per acre. | Baycor® 50% SC | 0.13 lb ai/A | 8 | 1.06 lb ai/A | None |

A tabular summary of the chemistry science assessments is presented in Table 6. The conclusions listed in Table 6 regarding the reregistration eligibility of bitertanol food/feed uses are based on the use patterns registered by the basic producer, Bayer CropScience.

| Table 6. Residue Chemistry Science Assessment for Reregistration of Bitertanol. | | | |
|---|---|---|---|
| GLN Data Requirements | Current Tolerances (ppm) [40 CFR] | Additional Data Needed? | MRID Nos. |
| 860.1200: Directions for Use | N/A = Not Applicable | No | None |
| 860.1300: Nature of the Residue - Plants | | | |
| - Bananas | N/A | No | 00025731, 00025734 |
| 860.1300: Nature of the Residue - Animals | N/A | No | None |
| 860.1340: Residue Analytical Method | | | |
| - Plant Commodities | N/A | No | 00025716, 00071187 |
| - Animal Commodities | N/A | No | None |
| 860.1360: Multiresidue Method | N/A | No[1] | None |
| 860.1380: Storage Stability Data | | | |
| - Plant Commodities | N/A | Yes[2] | None |
| - Animal Commodities | N/A | No | None |
| 860.1400: Magnitude of the Residue - Water, Fish, and Irrigated Crops | None established | No | None |
| 860.1460: Magnitude of the Residue - Food Handling | None established | No | None |
| 860.1480: Magnitude of the Residue - Meat, Milk, Poultry, and Eggs | None established | No | None |
| 860.1500: Crop Field Trials | | | |
| - Bananas | 0.2 [180.457] | Yes[3] | 00071186, 00071188, 00114273 |
| 860.1520: Processed Food/Feed | None established | No | None |
| 860.1650: Submittal of Analytical Reference Standards | N/A | Yes | None |
| 860.1850: Confined Accumulation in Rotational Crops | N/A | No | None |
| 860.1900: Field Accumulation in Rotational Crops | None established | No | None |

1. There was no information in the review documents regarding submittal of data for FDA multiresidue methods by the petitioner. However, the FDA PESTDATA database dated 11/2001 (PAM Volume I, Appendix I) indicates that bitertanol was completely recovered using Multiresidue Method Section 302 (Protocol D).
2. Storage stability data for bitertanol in/on bananas have not been submitted by the registrant, therefore, storage stability data are required (HED SOP 98.6). No information on the stability of residues in/on bananas during cold storage have been submitted. Additionally, no data were provided on how long the samples were stored from the submitted field trial studies conducted on bananas prior to analysis.
3. Additional data are required in order for the submitted field trials conducted in Costa Rica and Honduras to be acceptable. The number of trials, location of the trials within the countries, and the formulation type used. New field trial data are required for the SC formulation.
4. Analytical reference standards must be replenished as requested by the Repository.

## 860.1300 Nature of the Residue - Plants

The nature of the residue in plants is adequately understood based on acceptable metabolism

studies on apples and peanuts. The residues consisted primarily of the parent compound with traces of the metabolites bitertanol ketone and 4-hydroxybiphenol. The Agency concluded that the residue of concern is the parent (E. Zager, PP#0G2311, 6/30/1980).

Apple (MRID 00025731)

Golden Delicious variety apples were individually syringe-treated to run-off with a 50% wettable powder formulation at 0.015 g ai/100 mL (2 oz ai/100 gallons of water) of $^{14}$C-bitertanol labeled uniformly in the biphenyl ring. Sampling (6-9 apples) was immediately after drying, at 3, 7, 14, 23, 35, 42, and 49 days. The apples were initially subjected to several methanol rinses. The rinses were collected and analyzed. The apples were then separated into peel and pulp, portions of which were separately homogenized in liquid nitrogen. Subsamples of each portion were analyzed for total activity. Analysis was by thin-layer chromatography (TLC) using radiochromatogram scanning and autoradiography techniques.

The peel contained 95% of the total recovered radioactivity even after 49 days, the rest being in the pulp, showing that little migration had occurred. Surface residues decreased from 92% at day 0 to 43% at 49 days while the radioactivity in the peel organic extract increased from 7% to 44% of the total. Peel solids increased to 12% in the same interval, indicating some binding had occurred.

The two diasterioisomers of bitertanol were the major residues, in roughly equal proportions throughout the 49-day study. The level of the two combined in peel and pulp ranged from 98% of the total radioactivity at day 0 to 83% at 49 days, with lower surface residues and greater peel uptake by the end of that time. The two had penetrated the pulp by day 7 from which time residues were relatively constant at about 3% over the remaining test period. Minor metabolites were bitertanol ketone and 4-hydroxybiphenyl, together never exceeding 3% of the total radioactivity. Both of the metabolites were found in the peel. The half-life of bitertanol in this experiment was estimated at approximately 150 days.

Peanut (MRID 00025734)

To investigate the fate of bitertanol in peanuts, bitertanol labeled in the biphenyl ring system was applied to peanut plant leaves; to 1-month old peanut plants; to 2-month old peanut plants which were grown to maturity; and to the nutrient solution of growing peanut plants.

Peanut plant leaflets were treated with $^{14}$C-bitertanol and samples were taken at 3 and 14 days. At sampling the treated leaves were rinsed with methanol and subsequently extracted with dichloromethane and ACN. After 3 days, 1.7% of the applied $^{14}$C-bitertanol was absorbed, nearly all of which was identified as bitertanol by TLC. After 14 days, 3% of the applied $^{14}$C-bitertanol was found in the extract of the rinsed leaves, 82% of which was bitertanol and 14% unidentified polar material. The remainder of the applied $^{14}$C-bitertanol was recovered in the methanol rinse and consisted of 96% bitertanol. Total recoveries at each interval were 100-101%. This evidence shows that foliar application result in poor leaf absorption (96% unchanged bitertanol on the leaf surface after 14 days), with no observable volatility losses. Only very little translocation was observed, as well as little translocation to opposite leaves.

In another study, $^{14}$C-bitertanol uniformly labelled in the biphenyl ring was sprayed as a 50% WP formulation to both 1-month and 2-month old potted peanut plants at an approximate equivalent field rate of 2.7 lbs ai/A. Young plants were sampled at 12 and 28 days after treatment and the older plants and nuts after 10 weeks. In the 1-month old plants, after 12 days 72% and after 28 days 61% of the total recovered radioactivity was surface residue, the remainder were extractable residues (28% at 12 days and 39% at 28 days). In the 2-month old plants the distribution was 46% surface and 50% extractable.

In the 1-month peanut plants, bitertanol comprised 93% and 86% of the total residue at 12 days and 28 days, respectively. Metabolite R-1, apparently a glucoside of bitertanol, constituted 2-4% of the total residue. Traces (0.6%) of the metabolite 4-hydroxybiphenyl were found in extracted shoot solids of the 28-day sample. Little movement of $^{14}$C was observed from shoots to roots of the peanut plants.

In the 2-month peanut plants, residues in the foliage were 16.8 ppm bitertanol equivalent, with 75% of the plant residue actually identified as bitertanol. Metabolite R-1 constituted 6% of the residue and several other polar metabolites were observed with none constituting more than 1% of the residue. Residues in nut meats were 0.06 ppm bitertanol equivalent, which is 0.008% of the total plant residue.

In the root uptake study, young peanut plants were grown for 7 days in a nutrient solution fortified with biphenyl labeled $^{14}$C-bitertanol at 1 ppm followed by 7 days in an unfortified nutrient solution. A total of 94% of the administered radioactivity was recovered with 29% in the roots, 15% in the shoots, 40% in the fortified nutrient solution, and 11% in the non-fortified solution. Bitertanol constituted a total (roots and shoots) of 56% of the absorbed $^{14}$C while the metabolite R-1 (glucoside of bitertanol) accounted for 16%. Unextracted shoot solids were reacted with HI which released 9% of absorbed $^{14}$C as 4-hydroxybiphenyl. Radioactivity was concentrated in the veins, but distributed throughout the plant. No translocation to new growth occurred after removal of the fortified solution. Radioactivity in the non-fortified solution suggests desorption from within or from the surface.

Additional metabolism studies conducted with apples, cotton, and tomatoes have been submitted and are under review by the Agency. The apple (Report No. 94373, 3/16/1987) and cotton (Report No. 94382, 4/13/1987) metabolism studies were conducted with $^{14}$C-bitertanol labeled in the triazole ring. The tomato (Report No. M1731133-9, 1/15/2003) metabolism studies were conducted with $^{14}$C-bitertanol labeled in the triazole ring and in the phenyl ring.

The apple metabolism study shows that bitertanol is slowly metabolized when $^{14}$C-bitertanol labeled in the triazole ring is applied as the 50% WP at a field rate of 2 oz ai/100 gallons of water to apple fruit (less than 5% degradation in 49 days). All samples were radioassayed for $^{14}$C content by liquid scintillation counting (LSC). Quantitation of the parent and metabolites was achieved by LSC and identified by TLC and high performance liquid chromatography (HPLC). There was very little penetration of bitertanol into the fruit pulp throughout the 49 day sampling interval. The majority of the radiocarbon (91-98%) was located in the methanol rinse of the bag and fruit at every time interval. From 2 to 9% of the total residues were found to be associated with the washed peel fraction, i.e. not removed by the methanol rinse. No more than 1.5% was

found associated with the pulp fraction at any sampling interval with no trend toward increased residues over time. The majority of organoextractable residues from peel and pulp were identified as bitertanol with only 0.4-2% of the total residues being identified in the organosoluble fractions. Therefore, 96-99% of the total recovered residues were identified as intact parent bitertanol. An additional 0.1-0.5% of the total residue was unidentified as water soluble components.

The cotton metabolism study was conducted with $^{14}$C-bitertanol labeled in the triazole ring is applied as the 50% WP at a field rate of 250 g ai/ha in a volume of 300 liters to cotton plants at early bloom stage. An identical second treatment was made 14 days following second treatment. Samples were collected following the second treatment and at 7, 21, 35, and 63 days following the second application. Whole plants were stored frozen pending processing and analysis for 0- through 35-day intervals. The 63-day interval plants (mature sample) were separated into foliage, lint, calyx, seed, and hull and the comments also stored frozen pending processing and analysis. All samples were radioassayed for $^{14}$C content by liquid scintillation counting (LSC). Quantitation of the parent and metabolites was achieved by LSC and identified by TLC and HPLC. In mature cotton plants 63-days after the second application of $^{14}$C-bitertanol 91% of the total recovered radioactivity was associated with the foliage portion of the plant; 6% was associated with the calyx fraction; 1.3%, 1%, and 1% were associated with the lint, seed, and hull respectively. The majority of the recovered radiocarbon was was identified as intact bitertanol, amounting to a total of 79% of the mature harvest interval residue. The relative concentration of bitertanol isomers remained constant throughout the study period. There were trace amount of bitertanol acid and two metabolites tentatively identified as R-1 and R-2 present in the more mature time intervals, collectively accounting for 1.3% and 0.3% of the 35-day and 63-day interval samples respectively.

The metabolism of bitertanol was investigated in tomatoes following three spray applications at 600 g ai/ha for a total of 1800 g ai/ha. The active ingredient was $^{14}$C-bitertanol labeled in the triazole and was formulated as a SC. The first application was performed when mainly small tomatoes were visible and a few flowers were still open. The treatment was performed when most of the fruits had reached ca. 50% of the final size. The third treatment was three days before harvest, when ca. 30% of the tomatoes showed the typical ripe color. All samples were radioassayed for $^{14}$C content by LSC. Quantitation of the parent and metabolites was achieved by HPLC and identified by LC/MS, LC/MS/MS, and $^{1}$H-NMR spectroscopy experiments. The total radioactive residue (TRR) in tomatoes amounted for to 7.76 mg/kg, expressed as parent compound equivalents. Most of the radioactivity (97%) was extracted by surface wash with methanol. After homogenisation of the tomatoes and extraction with acn/water the residues were extracted quantitatively (99%). Unchanged parent compound accounted for 99% of the TRR. Two minor metabolites <0.1% were also detected, but due to the low portion of the TRR, they were not further analyzed. Judged by HPLC, the ratio of the two diasterioisomers of bitertanol remained nearly unchanged during the course of the study.

The other tomato study was conducted in the same way as noted above, however, the active ingredient was $^{14}$C-bitertanol labeled in the phenyl ring. The TRR amounted to 8.19 mg/kg, expressed as parent compound equivalents. Most of the radioactivity (96%) was extracted by surface wash with methanol. After homogenisation of the tomatoes and extraction with acn/water the residues were extracted quantitatively (99.6%). Unchanged parent compound accounted for 99.5% of the TRR and only a very small amount was detected as a metabolite (<0.1%). Judged

by HPLC, the ratio of the two diasterioisomers of bitertanol remained nearly unchanged during the course of the study.

In the plant studies bitertanol penetration from surface applications was minimal and there was little volatility. Residues are taken up by roots, although translocation into the plant is relatively low. There are some measurable but not major differences in absorption, translocation, and plant metabolism rates of the two diasterioisomeric forms of bitertanol. Bitertanol is by far the main plant residue, with low levels of bitertanol ketone and 4-hydroxybiphenyl.

No metabolism studies for bananas were submitted. However, HED has concluded that the nature of residues in bananas is likely similar to that in apples, cotton, tomatoes, and peanuts. Therefore, HED has determined that the bitertanol residues of concern in/on bananas for tolerance expression and for risk assessment are bitertanol.

Additionally, the Agency does have concern about the potential toxicity of 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, which are metabolites common to most of the triazole fungicides. To support the extension of existing and granting of new parent triazole-derivative fungicide tolerances, the Agency will be conducting a human-health assessment for aggregate exposure to 1,2,4-triazole.

**860.1300 Nature of the Residue - Livestock**

Bitertanol is not intended for application to livestock exported to the U.S. In addition, there are no feedstuffs associated with bananas. Therefore, no residue chemistry data are required under this guideline topic.

**860.1340 Residue Analytical Methods**

An analytical method for analysis of residues of bitertanol was submitted and reviewed in PP#2E2756. The submitted method is a modification of Mobay Chemical Corporation's Method 54166 for the analysis of Baycor® in apples. The modified method employs different gas chromatography (GC) parameters and column packing than the original Method 54166. The modified method consists of extracting the residues by blending successively with acetone followed by dichloromethane. The samples are then shaken three times with water in a separatory funnel. The water is discarded and the organic phase is collected, evaporated, and cleaned up using a Florisil column. Analysis is by GC using a nitrogen/phosphorus flame ionization detector (NPD). The method was validated by the Biological and Economic Analysis Division's (BEAD) Analytical Chemistry Branch (ACB) and the limit of quantitation was determined at 0.1 ppm (A. Burns, PP# 2E2756, 3/22/1983). The method trial was successfully performed on banana pulp and peels at fortification levels of 0.1 ppm and 0.2 ppm. Recoveries ranged from 78 to 88% for pulp samples, and from 70 to 98% for peel samples. The method was approved by the Agency for the enforcement of a tolerance in/on bananas and the results were forwarded to FDA for inclusion in PAM Volume II as Method I for bitertanol (M. Bradley, 9/15/92). The method has been received by FDA, however, it has not been compiled into PAM Volume II as of yet.

**860.1360 Multiresidue Methods**

There was no information in the review documents regarding submittal of data for FDA multiresidue methods by the petitioner. However, the FDA PESTDATA database dated 11/2001 (PAM Volume I, Appendix I) indicates that bitertanol was completely recovered using Multiresidue Method Section 302 (Protocol D).

**860.1380 Storage Stability**

Storage stability data for bitertanol in/on bananas have not been submitted by the registrant, therefore, storage stability data are required (HED SOP 98.6). No information on the stability of residues in/on bananas during cold storage have been submitted. Additionally, no data were provided on how long banana samples from the submitted field trials were stored prior to analysis.

**860.1400 Water, Fish, and Irrigated Crops**

Bitertanol is not intended for direct use on water and aquatic food and feed crops; therefore, no residue chemistry data are required under this guideline topic.

**860.1460 Food Handling**

Bitertanol is not intended for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline topic.

**860.1480 Meat, Milk, Poultry, and Eggs**

Bitertanol is not intended for application to livestock exported to the U.S. In addition, there are no animal feedstuffs associated with bananas. Therefore, no residue chemistry data are required under this guideline topic.

**860.1500 Crop Field Trials**

Residue data for bananas grown in Costa Rica and Honduras were provided by the petitioner. The petitioner indicated that these two countries are the only ones where bitertanol would be used. Bitertanol was applied to both bagged and unbagged bunches of green and ripe bananas at a rate of 4.2 oz ai/A/application, the maximum rate indicated in the product label. Samples of peel, pulp, and whole fruit were collected 3 days after the last of 9 treatments and 0 days after the last of 12 treatments. Washed and unwashed samples were analyzed for bitertanol by Method 54166, with modifications. No data were provided on how long the samples were stored prior to analysis. Control samples of washed or unwashed green peel, ripe peel, green pulp, and ripe pulp had no detectable (<0.01 ppm) residues of bitertanol. Recoveries for control samples of peel and pulp from green and ripe bananas fortified at levels of 0.02 - 0.10 ppm were 56 to 120% (A. Smith, PP#2E2756, 1/28/83).

Residue data were reported for both washed and unwashed samples of bagged and unbagged bananas. The results are summarized below in Table 7. All residues identified in the bagged samples were below the tolerance level of 0.2 ppm. In the bagged banana trials, after 9 applications of bitertanol, the highest residue in a washed sample was 0.5 ppm (green and ripe

peel) and the highest residue in an unwashed sample was 0.01 ppm (green pulp). After 12 applications of bitertanol, the highest residue in a washed sample was 0.15 ppm (green peel) and the highest residue in an unwashed sample was 0.12 ppm (ripe peel). Residues were detected above the tolerance level of 0.2 ppm in the unbagged samples. In the unbagged banana trials, the highest residues detected after 9 applications were 0.45 ppm (ripe peel) in washed samples and 0.53 ppm (green peel) in unwashed samples. After 12 applications, the highest residues detected were 0.73 ppm (green peel) in washed samples and 0.76 ppm (green peel) in unwashed samples. With few exceptions, residues were higher in washed samples than in unwashed samples for both bagged and unbagged bananas. No explanation was provided for the higher residues found in washed samples.

The petitioner originally had requested the establishment of a tolerance for residues of bitertanol at 0.5 ppm. However, based on the results of the field trials, HED concluded that a tolerance of 0.5 ppm was excessive and recommended that a tolerance of 0.2 ppm be proposed (A. Smith, Memorandum, 1/28/83). The petitioner submitted a revised tolerance petition proposing a tolerance for residues of bitertanol of 0.2 ppm, which was later accepted by HED (A. Smith, PP#2E2756, 9/14/83). In order to harmonize with Codex, the established tolerance should be increased to 0.5 ppm.

It is noted that the number of trials, location of the trials within the countries were not specified, and the formulation type was not specified. The petitioner had originally proposed the use of a 50% WP and a 30% emulsifiable concentrate (Baycor® 300 EC). The use of the emulsifiable concentrate formulation was later withdrawn by the registrant (G. E. Brussell, PP#2E2756, 10/13/83).

At the time the import tolerance for bitertanol on bananas was established, HED provided case-by-case advice on adapting data requirements for field trials to import situations. Since then, guidance on data requirements for import tolerance petitions has been issued. In the Federal Register of June 1, 2000 (65 FR 35069; FRL-6559-30), EPA provided detailed guidance on applying current U.S. data requirements for the establishment or continuance of tolerances for pesticide residues in or on imported foods. In addition, in 2003, Canada, Mexico and the United States jointly issued a guidance document on the data requirements needed to meet the North American Free Trade Agreement (NAFTA) standards for the establishment of pesticide import tolerances or maximum residue levels in the NAFTA countries (68 FR 18638; FRL-7299-1). The NAFTA guidance document is consistent with the 2000 U.S. guidance. In general, the residue chemistry requirements for import tolerances listed in the NAFTA guidance document are similar to those for any other tolerance issued by the NAFTA countries. However, the NAFTA guidance document details a procedure for determining the minimum number and location of field trials, based on the maximum consumption of the commodity as a percentage of the U.S., Canadian, or Mexican diet, and the maximum relative amount imported into the U.S., Canada, or Mexico from outside of North America. The NAFTA guidance document also indicates that field trials generally will need to be conducted in all countries whose exports comprise at least 5% of the total amount of a specific commodity imported into any of the North American countries where a tolerance is being sought. It is noted that the field trials currently being conducted with the SC formulation should adhere to all guidance documents.

**Table 7. Summary of Residues from the Crop Field Trials with Bitertanol.**

| Crop Matrix | Applic. Rate (lb ai/A) | Number of Applications | PHI (days) | Residues (ppm) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Bagged | | Unbagged | |
| | | | | Washed samples | Unwashed samples. | Washed samples | Unwashed samples. |
| Green peel | 4.2 oz ai/A | 9 | 3 | 0.05 | <0.01 | 0.41 | 0.53 |
| Green pulp | | | | 0.01 | 0.01 | 0.09 | 0.11 |
| Green fruit | | | | 0.03 | <0.01 | 0.22 | 0.24 |
| Ripe peel | | | | 0.05 | <0.01 | 0.45 | 0.25 |
| Ripe pulp | | | | 0.02 | <0.01 | 0.11 | 0.06 |
| Ripe fruit | | | | 0.03 | <0.01 | 0.23 | 0.13 |
| Green peel | 4.2 oz ai/A | 12 | 0 | 0.05, 0.15 | 0.04 | 0.09- 0.73 | 0.10-0.76 |
| Green pulp | | | | 0.01, 0.02 | 0.01 | 0.03, 0.17 | 0.03, 0.08 |
| Green fruit | | | | 0.03, 0.06 | 0.02 | 0.05, 0.36 | 0.06-0.33 |
| Ripe peel | | | | 0.03-0.08 | 0.03-0.12 | 0.05, 0.51 | 0.03-0.32 |
| Ripe pulp | | | | <0.01, 0.02 | 0.01 | 0.02, 0.14 | <0.01, 0.08 |
| Ripe fruit | | | | 0.01-0.04 | 0.02-0.05 | 0.03-0.28 | 0.01-0.17 |

**860.1520 Processed Food and Feed**

There are no processed commodities associated with bananas. Therefore, no residue chemistry data are required under this guideline topic.

**860.1650 Submittal of Analytical Reference Standards**

An analytical reference standard for bitertanol was submitted by Bayer in December of 2004 and expires October of 2010. The standard is available at the EPA National Pesticide Standards Repository.

**860.1850 Confined Accumulation in Rotational Crops**

Rotational crop studies are not required for uses of pesticides on bananas (HED SOP 96.6).

**860.1900 Field Accumulation in Rotational Crops**

Rotational crop studies are not required for uses of pesticides on bananas (HED SOP 96.6).

**Tolerance Reassessment Summary**

The tolerance for residues of bitertanol in/on plant commodities is expressed in terms of residues of bitertanol *per se* [β-([1,1 '-biphenyl]-4-yloxy)-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-

ethanol].

A summary of the bitertanol tolerance reassessment for bananas is presented in Table 8.

Tolerances Listed Under 40 CFR §180.457:

A tolerance has been established under 40 CFR §180.457 for residues of bitertanol in/on bananas imported into the U.S. Field trials conducted in Costa Rica and Honduras showed residues below the existing tolerance level of 0.2 ppm. In order to harmonize with Codex, the established tolerance should be increased to 0.5 ppm.

Since the tolerance for bitertanol is an import tolerance, it should be listed in a separate subsection of 40 CFR indicating that there are no U.S. registrations for bitertanol.

**Table 8. Tolerance Summary for Bitertanol.**

| Commodity | Established/Proposed Tolerance (ppm) | Recommended Tolerance (ppm) | Comments *[correct commodity definition]* |
|---|---|---|---|
| Banana (whole) | 0.20 (established) | 0.5 | Tolerance should be listed in a separate subsection of 40 CFR indicating that there are no U.S. registrations associated with bitertanol. *[Banana]* |

## Codex/International Harmonization

The Codex Alimentarius Commission has established a maximum residue limit (MRL) for bitertanol residues in/on bananas at 0.5 mg/kg. The Codex MRL for bitertanol is expressed in terms of residues of bitertanol only, as is the U.S. tolerance expression. Various enforcement methods are listed for bitertanol under the Codex system including PAM Multiresidue Method Section 302 (Protocol D).

It is EPA's policy to harmonize its tolerances with the levels established by Codex provided that the Agency has sufficient information to make a determination that the Codex MRLs will be protective of the health of the U.S. public and meet FFDCA standards. FQPA requires EPA to publish a notice for public comment whenever the Agency establishes a tolerance that differs from an established Codex MRL. The established tolerance should be reassessed to 0.50 ppm to harmonize with Codex as the dietary exposure and risk are not of concern (S. Ary, D302880, 11/2/2005).

## Bibliography

NAFTA Guidance Document on Data Requirements for Tolerances on Imported Commodities. April 2003.
(http://yosemite.epa.gov/opp/naftatwg.nsf/0/ff1cbe90259cd6b985256d0900705b7e/$FILE/NAFTA%20Import%20Tolerances%20Document.PDF)

65 FR 35069. Pesticides; Guidance on Pesticide Import Tolerances and Residue Data for Imported Food; Request for Comment. June 1, 2000 (Volume 65, Number 106). (http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-01/p13708.htm)

68 FR 18638. Pesticides; North American Free Trade Agreement Guidance Document on Requirements for Tolerances on Imported Commodities; Notice of Availability. April 16, 2003 (Volume 68, Number 73). (http://www.epa.gov/fedrgstr/EPA-PEST/2003/April/Day-16/p9338.htm)

HED Standard Operating Procedure (SOP) 98.6. Data requirements for Import Tolerances (12/3/1998).

## Study Citations

**Table 9. Agency Memoranda Citations.**

| Date | Barcode | ID Number | From | To | MRID Nos. | Subject |
|---|---|---|---|---|---|---|
| 6/30/1980 | | PP# 0G2311 | E. Zager | H.M. Jacoby | 00025731, 00025734, 00025716, 00071187 | PP#0G2311. Baycor® on apples, pears and peanuts. Evaluation of Analytical Methods and Residue Data. |
| 1/28/1983 | | PP# 2E2756 | A. Smith | H.M. Jacoby | 00071186, 00071188, 00114273 | PP#2E2756: Baycor® in Bananas. Evaluation of residue data and analytical method. |
| 3/22/1983 | | PP# 2E2756 | A. Burns | A. Smith | 00025716, 00071187 | Report on Method trial. |
| 4/27/1983 | | PP# 2E2756 | A. Smith | H.M. Jacoby/ Toxicology Branch | 00025716, 00071187 | PP#2E2756: Baycor® in Bananas. Report on Method trial. |
| 8/10/1983 | | PP# 2E2756 | G. E. Brussell Mobay Chemical Corporation | H.M. Jacoby | | Baycor® 50% Wettable Powder and Baycor® 300 EC. Pesticide Petition No. 2E2756. Tolerance for Baycor® in or on Bananas. |
| 9/14/1983 | | PP# 2E2756 | A. Smith | H.M. Jacoby | | PP#2E2756: Baycor® in Bananas. Amendment of 5/26/83. |
| 10/13/1983 | | PP# 2E2756 | G. E. Brussell Mobay Chemical Corporation | H.M. Jacoby | | Baycor® on Bananas. Pesticide Petition No. 2E2756 |
| 9/15/1992 | | | M. Bradley | A. Marcotte FDA | | Letter to FDA. Submission of Method I for bitertanol for inclusion in PAM Volume II. |
| 11/2/2005 | D302880 | | S. Ary | C. Jarvis and R. Louie | | Bitertanol. Acute and Chronic Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED) Document. |

## Master Record Identification Numbers

00025716 Obrist, J.J.; Nichols, S.S. (1979) An Interference Study for the Baycor(TM) Residue Method for Apples and Peanuts: Report No. 68311. (Unpublished study received Dec 21, 1979 under 3125- EX-168; submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL:099186-F)

00071187 Obrist, J.J.; Nichols, S.S. (1980) An Interference Study for the Baycor(TM) Residue Method for Apples and Peanuts: Report No. 68311. Rev. (Unpublished study received Feb 2, 1981 under 1E2468; submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL:099905-C)

00025731 Puhl, R.J.; Hurley, J.B. (1979) The Metabolism of Baycor(TM)-biphenyl-UL-14C in Apple Fruit: Report No. 68305. (Unpublished study received Dec 21, 1979 under 3125-EX-168; submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL:099185-O)

00025734 Puhl, R.J.; Hurley, J.B. (1979) Metabolism of Baycor(TM)-biphenyl-UL-14C in Peanut Plants: Report No. 68310. (Unpublished study received Dec 21, 1979 under 3125-EX-168; submitted by Mobay Chemical Corp., Kansas City, Mo.; CDL:099185-R)

00071186 Mobay Chemical Corporation (1980) Synopsis of Baycor: Residue Chemistry on Bananas. Summary of studies 099905-C and 099905-D. (Unpublished study received Feb 2, 1981 under 1E2468; CDL: 099905-A)

00071188 Mobay Chemical Corporation (1980) (Residue of Baycor (TM): Bananas): Report No. 68896. (Compilation; unpublished study, including report nos. 68897, 68898, 68899 received Feb 2, 1981 under 1E2468; CDL:099905-D)

00114273 Mobay Chemical Corp. (1982) Addition No. 1 to the Brochure Entitled: Baycor Residue Chemistry on Bananas: Document No. AS- 82-2104. (Compilation; unpublished study received Sep 15, 1982 under 2E2756; CDL:071088-A)