Read 4/14/94

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

APR 14 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Thiabendazole (ID 060101). Residue Chemistry Data Requirement 171-4(k) for bananas. Barcode: D196149; CBRS No. 12715; MRID No.: 428687-01: Case No. 2670.

FROM: Francis B. Suhre, Section Head
Special Review Section I
Chemistry Branch II--Reregistration Support
Health Effects Division (7509C)

THRU: Edward Zager, Chief
Chemistry Branch II--Reregistration Support
Health Effects Division (7509C)

TO: Barbara Briscoe, Section Head
Reregistration Branch
Special Review and Reregistration Division (7508W)

Attached is a review of registrant's response to the Residue Chemistry Data Requirement for thiabendazole Magnitude of the Residue Studies for bananas [171-4(k)]. This information was reviewed by Dynamac Corporation under the supervision of CBRS/HED. The data assessment has undergone secondary review in the Branch and has been revised to reflect Branch policies.

CBRS makes the following conclusions with respect to the submitted studies:

The submitted data from the banana residue study are insufficient to satisfy reregistration requirements and support the existing import tolerances because the spray mist application does not represent the most aggressive postharvest application method (i.e., dip and cascade drench) allowed on bananas targeted for export to the U.S. In addition, CBRS has concluded that BNZ and its conjugates are to be included in the tolerance expression. The following additional data are required:

- After adequate analytical methodology is developed that is capable of detecting BNZ and its conjugates, residue data for thiabendazole and BNZ must be submitted reflecting maximum registered use patterns (i.e., using Mertect® 340F and Mertect® 20-S formulations applied separately as a cascade drench and dip at a rate of 400 ppm). A copy of the product label for Mertect 340-F® must also be provided. Samples should be collected at the shortest likely interval between treatment and arrival to the U.S. borders, and information regarding minimum transit time must be documented.

If you need additional information, please advise.

cc: RF, SF, List B Rereg. F., Circ., Dynamac.
RDI: MMetger:04/14/94;EZager:04/14/94.

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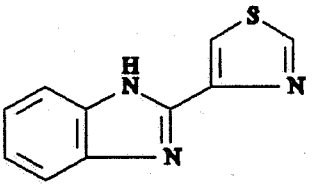
THIABENDAZOLE



(Shaughnessy No. 060101; Case 2670)

(CBRS No. 12715; DP Barcode D196149)

Task 4

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

BACKGROUND

The Thiabendazole Phase IV Reviews (C. Olinger, 2/21/91) required data depicting the magnitude of residues of thiabendazole and its regulated metabolites in/on bananas and banana pulp following applications according to the foreign maximum registered use patterns of representative thiabendazole formulations for bananas which are targeted for export to the USA. The tests were to be conducted in all countries in which thiabendazole may be used on bananas. Additionally, translated labels and documentation confirming that the cultural practices are representative of the region were required with the residue data.

A thiabendazole post-harvest protocol was approved by the Agency (C. Olinger, CBRS No. 6781, 7/11/90). The Agency (C. Olinger, CBRS No. 8181, 7/16/91) further determined that the analysis for thiabendazole *per se* was acceptable in residue studies pertaining to post-harvest uses of thiabendazole on pome and citrus fruits, pending the outcome of plant metabolism studies. The qualitative nature of the residue in plants is now adequately understood (L. Cheng, CBRS No. 8192, 3/11/92); the residues of concern in plants are the parent compound thiabendazole (TBZ) and benzimidazole (BNZ) and its conjugates.

The Agency held a meeting with Merck Research Laboratories to discuss the design of the banana field trials (see D. Edwards memorandum, 1/28/92, no CBRS No. Assigned). The registrant indicated plan to support postharvest uses on bananas using the Mertect® 340F (42.28% ai) and Mertect® 20-S (20% ai as hypophosphite salt) formulations applied as a spray mist, cascade drench, and dip at rates of 200 and 400 ppm. The registrant indicated that the following countries use thiabendazole for postharvest treatment on bananas exported to the USA: Costa Rica, Guatemala, Honduras, Nicaragua, Panama, Columbia, and Ecuador.

CBRS advised the registrant to conduct the field studies using both formulations and the most aggressive application methods (dip and cascade drench) at the highest permissible rate. In addition, CBRS stated that samples should be collected at the shortest likely interval between treatment and arrival to the U.S. borders, and that information regarding minimum transit time must be documented.

Merck Research Laboratories has subsequently submitted six volumes of data (1993; MRID 42868701) depicting the magnitude of thiabendazole residues in/on bananas and banana pulp. Samples from these trials were only analyzed for residues of thiabendazole *per se* because according to the registrant, a postharvest orange metabolism study reviewed in PP#8F0724 and PP#1F1031 identified only the parent. These submissions are reviewed herein to determine their adequacy in fulfilling residue chemistry data requirements for thiabendazole reregistration. The Conclusions and Recommendations stated in this document pertain only to the magnitude of thiabendazole residues in/on bananas and banana pulp; other data requirements stated in the Phase IV Reviews are not addressed herein.

Tolerances for residues of thiabendazole [2-(4-thiazolyl)benzimidazole] in/on raw and processed plant commodities are currently expressed in terms of thiabendazole *per se* [40 CFR §180.242(a), §185.5550, and §186.5550(a)]. Methods are available for determining residues of thiabendazole *per se* in/on plant commodities and are listed in PAM, Vol. II as Methods I, A, B, and C. The Agency (L. Cheng, CBRS No. 8192, 3/11/92; and R. Perfetti, CBRS 10954, 4/15/93) has determined that a method must be developed for plants that is capable of quantifying free and conjugated benzimidazole.

The Codex MRL and U.S. tolerance definitions for thiabendazole residues are both currently expressed in terms of thiabendazole *per se*. The established Codex MRL (CXL) and U.S. tolerance for bananas are identical (3 ppm). Once the U.S. tolerance expression is revised to include residues of benzimidazole and its conjugates, the two systems will no longer be compatible with regards to expression.

CONCLUSIONS AND RECOMMENDATIONS

1. The submitted data from the banana residue study are insufficient to satisfy reregistration requirements and support the existing import tolerances because the spray mist application did not represent the most aggressive postharvest application methods (i.e., dip and cascade drench) allowed on bananas targeted for export to the U.S. In addition, CBRS has concluded that BNZ and its conjugates are to be included in the tolerance expression. The following additional data are required:

- After adequate analytical methodology is developed that is capable of detecting BNZ and its conjugates, residue data for thiabendazole and BNZ must be submitted reflecting maximum registered use patterns (i.e., using Mertect® 340F and Mertect® 20-S formulations applied separately as a cascade drench and dip at a rate of 400 ppm). A copy of the product label for Mertect 340-F® must also be provided. Samples should be collected at the shortest likely interval between treatment and arrival to the U.S. borders, and information regarding minimum transit time must be documented.

2. The conclusion cited above (Conclusion No. 1), with regard to the need for residue data on the metabolite BNZ on bananas, is consistent with the requirements specified in a recent evaluation of apple and pear residue studies (R. Perfetti, CBRS No. 10954, 4/15/93) involving postharvest application.

3. Although incomplete, data from the banana study indicate that residues of thiabendazole *per se* are not likely to exceed the established tolerances of 3 and 0.4 ppm in/on bananas and banana pulp following postharvest spray mist application of the Mertect® 20-S and Mertect® 340F formulations to bananas at 1x.

4. Data collection and tolerance enforcement methodology capable of quantifying free and conjugated BNZ must be developed. Methods proposed for enforcement must undergo independent laboratory validation prior to being submitted for EPA laboratory validation.

5. The submitted storage stability data indicate that residues of thiabendazole *per se* are stable at -20 C for three months in/on fortified samples of whole green bananas and ripe banana pulp. The required banana residue study must be accompanied by supporting storage stability data for thiabendazole and BNZ.

DETAILED CONSIDERATIONS

Residue Analytical Methods

In conjunction with the submitted banana field residue study, Merck Research Laboratories submitted descriptions and concurrent method recovery data (1993; MRID 42868701) for an analytical method (Merck Standard Assay Procedure, S.A.P. 500-B-011,) for determining residues of thiabendazole *per se* in/on bananas. The submitted method is a modification of Method A in PAM Vol. II.

Briefly, whole green banana and ripe banana pulp samples are homogenized and extracted with ethyl acetate and then sequentially washed with ethyl acetate containing 2 N NaOH and NaCl-saturated

water. The ethyl acetate fraction is acidified with 0.1 N HCl, centrifuged, and the acid layer is mixed with 2 N NaOH, 2 N sodium acetate, NaCl, and ethyl acetate. The mixture is centrifuged and an aliquot of the ethyl acetate fraction is acidified with 0.1 N HCl. After centrifugation, an aliquot of the acid layer is analyzed spectrofluorometrically for thiabendazole. For whole green bananas, the limit of detection (LOD) is 0.01 ppm with a limit of quantitation (LOQ) of 0.02 ppm. For ripe banana pulp, the LOD and LOQ are 0.005 ppm and 0.01 ppm, respectively.

The registrant provided concurrent method recoveries. Untreated control samples of whole green bananas and ripe banana pulp were fortified with thiabendazole at 0.01-4.0 ppm. Apparent residues were nondetectable in/on whole green bananas (<0.01 ppm; two samples) and ripe banana pulp (<0.005 ppm; two samples). The method recoveries are presented in Table 1. Sample calculations, raw data, and representative fluorescence spectra were provided.

The recovery data for method S.A.P. 500-B-011 are adequate for data collection in determining residues of thiabendazole *per se* in/on bananas. However, CBRS has concluded that benzimidazole (BNZ) and its conjugates are to be included in the tolerance expression. Therefore, data collection and tolerance enforcement methodology capable of quantifying free and conjugated BNZ must be developed. Methods proposed for enforcement must undergo independent laboratory validation prior to being submitted for EPA laboratory validation.

Table 1. Concurrent method recoveries of thiabendazole from control samples fortified with thiabendazole.

Commodity	Fortification Level (ppm)	% Recovery [a]
Whole green banana	0.02, 0.05	100-102
	0.10, 0.20	98-109
	1.00, 4.00	96-105
Ripe banana pulp	0.01, 0.025	85-92
	0.05, 0.10	95-115
	0.10, 0.40	95-102

[a] Recovery values were corrected for thiabendazole residues in/on control samples; samples were analyzed in duplicate.

Storage Stability Data

Treated samples of whole green bananas from the submitted magnitude of the residue study were shipped from Honduras in refrigerated containers. Upon arrival in the U.S. in ca. 6 days, subsamples of green bananas were homogenized and stored frozen at ca. -20 C for 24 days

before shipment to Merck Research Laboratories (Rahway, NJ) for residue analysis. Whole green bananas in another subsamples were ripened, processed into pulp, and stored frozen ca. -20 C for 19 days before shipment to the same analytical laboratory. At Merck, the frozen samples were stored frozen at ca. -15 C until analyses. We estimate that analyses were completed within 3 months after postharvest treatment of thiabendazole on bananas.

In conjunction with the submitted banana field residue study, Merck Research Laboratories submitted data (1993; MRID 42868701) depicting the frozen stability of fortified residues of thiabendazole *per se* in/on bananas. Untreated homogenized whole green bananas and ripe banana pulp were blended with water, transferred to plastic containers, and separately fortified with thiabendazole at 0.5 and 0.1 ppm, respectively. The fortified samples were shaken for ca. 60 minutes prior to being stored at -20 C. The banana samples were analyzed for residues of thiabendazole *per se* at 0-, 1-, 2-, and 3-month intervals using the previously described spectrofluorometric method (S.A.P. 500-B-011). The recoveries of thiabendazole from fortified control samples are presented in Table 2.

The submitted storage stability data indicate that fortified residues of thiabendazole *per se* are stable at -20 C for three months in/on whole green bananas and ripe banana pulp. However, CBRS has concluded that BNZ and its conjugates are to be included in the tolerance expression. Therefore, the required banana residue study must be accompanied by supporting storage stability data for BNZ in addition to the parent thiabendazole.

Table 2. Stability of thiabendazole in/on bananas fortified with thiabendazole and stored at -20 C.

Commodity	Storage Interval	% Recovery [a]
Whole green bananas	0	98, 99
	1	97, 98
	2	96, 97
	3	96, 98
Ripe banana pulp	0	94, 100
	1	95, 98
	2	96, 99
	3	95, 98

[a] Recovery values represent two samples analyzed in duplicate; values were not corrected for method recoveries.

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Magnitude of the Residue in Bananas

The established tolerances for residues of thiabendazole *per se* in/on bananas and banana pulp are 3 and 0.4 ppm, respectively [40 CFR §180.242(a)].

The registrant provided a specimen (Spanish with English translation) of the label for Mertect® 20-S (20% ai as hypophosphite salt; 220 g ai/L). This product is registered for use on bananas grown in Costa Rica, Guatemala, Honduras, Nicaragua, and Panama for a single postharvest treatment of green bananas via spray to run-off, cascade, or dip application techniques at 200-400 ppm ai. No specimen label was provided for the Mertect® 340F (42.28% ai).

Merck Research Laboratories submitted data (1993; MRID 42868701) from two tests conducted in Honduras (Corozal and Las Flores) depicting the magnitude of thiabendazole residues in/on whole green bananas and ripe banana pulp. Harvested bananas were washed, and spray misted with MERTECT 20-S® or MERTECT 340-F® under pressure in a chamber at 400 ppm (1x the maximum rate). Untreated bananas were directly spray misted with water and alum. The treated and control samples were packed in refrigerated (11-25 C) commercial containers and were transported by ship to the U.S. Upon arrival at Gulfport, MS, subsamples were taken for residue analysis and for ripening and processing. The whole green bananas were homogenized and stored at -20 C and the remaining green bananas were shipped to Pelican Tomato Ripening Company (Jefferson, LA) for commercial ripening and later to Pest Management Enterprises, Inc (Cheneyville, LA) for processing. At the processing facility, the ripened bananas were peeled (without washing) and homogenized into pulp. The processed pulp was stored at ca. -20 C until it was shipped to Merck Research Laboratories (Rahway, NJ) for analysis.

The results of this residue study are presented in Table 3. Apparent residues were <0.01 ppm (non-detectable) and <0.005 (non-detectable) in/on eight untreated samples (analyzed in duplicate) each of green banana and ripe banana pulp, respectively.

Table 3. Residues of thiabendazole found in/on whole green bananas and ripe banana pulp following direct spray mist treatment at 1x.

Commodity	Test Site	Formulation	Residues (ppm) [a]
Whole green banana	Las Flores	Mertect 20-S®	0.92-1.26
	Las Flores	Mertect 340-F®	0.64-0.88
	Corozal	Mertect 20-S®	0.61-1.05
	Corozal	Mertect 340-F®	0.60-1.03
Ripe banana pulp	Las Flores	Mertect 20-S®	0.005-0.029
	Las Flores	Mertect 340-F®	0.003-0.031
	Corozal	Mertect 20-S®	0.006-0.017
	Corozal	Mertect 340-F®	0.014-0.028

[a] Residue values represent the range of the highest of duplicate analyses of 10 samples; residue values were not corrected for method recoveries.

These data indicate that residues of thiabendazole *per se* are not likely to exceed the established

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tolerances of 3 and 0.4 ppm in/on bananas and banana pulp following postharvest spray mist application of the Mertect® 20-S and Mertect 340-F® formulations to bananas at 1x. However, these data are insufficient to satisfy reregistration requirements and support the existing import tolerances because the spray mist application did not represent the most aggressive postharvest application methods (i.e., dip and cascade drench) allowed on bananas targeted for export to the U.S. In addition, CBRS has concluded that BNZ and its conjugates are to be included in the tolerance expression. After adequate analytical methodology is developed that is capable of detecting BNZ and its conjugates, residue data for thiabendazole and BNZ must be submitted reflecting maximum registered use patterns (i.e., using Mertect® 340F and Mertect® 20-S formulations applied separately as a cascade drench and dip at a rate of 400 ppm). A copy of the product label for Mertect 340-F® must also be provided. Samples should be collected at the shortest likely interval between treatment and arrival to the U.S. borders, and information regarding minimum transit time must be documented.

EPA MEMORANDA CITED IN THIS REVIEW

CBRS No.	6781
DP Barcode:	None
Subject:	Thiabendazole Post-harvest Protocols I.D. No. 60101
From:	C. Olinger, CB II, HED
To:	F. Rubis, SRRD
Dated:	7/11/90
MRID(s):	None

CBRS No.	None
DP Barcode:	D165692
Subject:	Thiabendazole: Time Extension Request and Magnitude of Residue for Post-harvest Treatments Inquiry; Chemical No. 60101; Case No. 2670; Branch No. 8181.
From:	C. Olinger, CB II, HED
To:	F. Rubis, SRRD
Dated:	7/19/91
MRID(s):	None

CBRS No.:	None
DP Barcode:	D165692
Subject:	Magnitude of the Residue Studies for Registration of Thiabendazole on Bananas
From:	D. Edwards, CBTS, HED
To:	Thiabendazole Reregistration File
Dated:	1/28/92

MRID(s): None

CBRS No.: 8192
DP Barcode: D165718
Subject: Thiabendazole. Phase V Review. Metabolism Studies: Wheat, Soybeans, and Sugar Beet
From: L. Cheng, CB II, HED
To: F. Rubis, SRRD
Dated: 3/11/92
MRID(s): 41872901, 41872902, 41872903, and 41872904

CBRS No. 10954
DP Barcode: D185173
Subject: Response to the Thiabendazole Phase IV Review: Residue Chemistry Data (MRID #'s 42515801 and -02)
From: R. Perfetti, CB II, HED
To: F. Rubis and E. Saito, SRRD
Dated: 4/15/93
MRID(s): 42515801 and 42515802

MASTER RECORD IDENTIFICATION NUMBERS

The citation for the MRID document referred to in this review is presented below.

42868701 Norton, J.A. (1993) Determination of the Magnitude of Residues of the Fungicide Thiabendazole in Green and Ripened Banana Fruit Imported from Honduras. Laboratory Project Identification No. 93768. Unpublished study conducted by Merck Research Laboratories, Rahway, NJ and submitted by Merck & Co., Inc., Three Bridges, NJ. 869 p.