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

APR 15 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response to the Thiabendazole Phase IV Review: Residue Chemistry Data (MRID #'s 42515801 and -02, CBRS # 10,954, Barcode: D185173).

FROM: R. B. Perfetti, Ph.D., Chemist RBPerfetti
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THRU: E. Zager, Chief
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TO: F. Rubis
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and

E. Saito, Chief
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Attached is a review of Residue Chemistry data submitted by Merck Research Laboratories in response to the thiabendazole Phase IV review. This review was completed by Acurex Corporation under supervision of CBRS, HED. It has undergone secondary review in the branch and has been revised to reflect Agency policies.

A revised Tentative Residue Summary Sheet is included.

If you need additional input please advise.

Attachment 1: Thiabendazole Residue Chemistry Data Review.

cc (With Attachment 1): RBP, Thiabendazole List B File, Thiabendazole Subject File, Circ. and Acurex.

cc (Without Attachments): RF.

THIABENDAZOLE
(Chemical Codes 060101 & 060102)
(CBRS No. 10954; DP Barcode D185173)

TASK 2B

Phase 5 - Reregistration Review
Residue Chemistry

January 29, 1993

Contract No. 68-DO-0142

Submitted to:

U.S. Environmental Protection Agency
Arlington, VA 22202

Submitted by:

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THIABENDAZOLE

(Chemical Codes 060101 & 060102)

(CBRS No. 10954; DP Barcode D185173)

PHASE 5 - REREGISTRATION REVIEW RESIDUE CHEMISTRY

Task 2B

BACKGROUND

The Thiabendazole Phase 4 review dated 2/91 required data depicting residues of thiabendazole and its regulated metabolites in or on apples and pears following sequential postharvest treatment with thiabendazole as a dip and a wax application at concentrations of 1000 ppm and 2000 ppm, respectively. Data were also required depicting residues of thiabendazole and its regulated metabolites in apple commodities processed from apples bearing measurable weathered residues. 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 of 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. In response, Merck Research Laboratories submitted data (1992; MRIDs 42515801 and 42515802) depicting residues of thiabendazole in or on pears, apples, and processed apple commodities. These submissions are reviewed here to determine their adequacy in fulfilling residue chemistry data requirements. The Conclusions and Recommendations stated in this review pertain only to thiabendazole residues in or on pears, apples, and processed apple commodities.

The nature of the residue in plants is adequately understood. The residues of concern are the parent compound thiabendazole and benzimidazole (BNZ) and its conjugates. Methods are available for determining residues of thiabendazole per se in or on plant commodities and are listed in PAM, Vol. II, as Methods I, A, B, and C. The Agency has determined that a method must be developed for plants that is capable of measuring BNZ conjugates (L. Cheng; CBRS No. 8192, 3/11/92).

thiabendazole
benzimidazole (BNZ)

Tolerances for residues of thiabendazole (2-(4-thiazolyl)benzimidazole) in or 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)], and tolerances in animal commodities are expressed in terms of the combined residues of thiabendazole and its metabolite, 5-hydroxy-thiabendazole, [40 CFR 180.242(b)]. The Codex MRL's are expressed in the same way. U.S. tolerances and Codex MRLs (CXL) for thiabendazole residues in/on apples and pears are identical (10 ppm). However, the Agency has determined that the residue to be regulated in plants is thiabendazole and benzimidazole. Therefore, U.S. tolerances are will not be compatible with the corresponding Codex MRLs for plant commodities in the future.

CONCLUSIONS/RECOMMENDATIONS

1. The residue studies on apples and pears and the apple processing study are not adequate. CBRS has concluded that BNZ and conjugates are to be included in the tolerance expression. After adequate analytical methodology is developed that is capable of detecting BNZ and conjugates, residue data for BNZ must be submitted reflecting registered uses on apples and pears and from an apple processing study.

2. Data from the apple processing study indicate that thiabendazole residues concentrate approximately 12x in dry apple pomace. However, data are needed to determine the potential for concentration of BNZ. The appropriate level for a feed additive tolerance will be determined after (i) the newly defined apple tolerance level is determined, and (ii) data are available to determine the potential for concentration of combined thiabendazole and BNZ residues.

3. 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 lab validation.

4. The submitted storage stability data indicate that thiabendazole per se is stable in apples, apple juice, and

dried pomace for at least 273 days (9 months) at -15 C. The required residue and processing studies must be accompanied by supporting storage stability data for thiabendazole and BNZ.

DETAILED CONSIDERATIONS

Residue Analytical Methods

In conjunction with the residue studies, Merck Research Laboratories submitted analytical method descriptions (1992; MRIDs 42515801 and 42515802). Thiabendazole residues were determined using Merck Standard Assay Procedure, S.A.P. 500-A-011, a modification of Method I in PAM Vol. II. Method I has undergone a successful FDA validation test; recoveries of thiabendazole were 81-100% from samples of peeled fruit fortified at 0.04-0.08 ppm and were 84-105% from samples of whole fruit fortified at 2-4 ppm. For Method S.A.P. 500-A-011, residues of homogenized fruit samples were determined by extraction into EtOAc (3x). The pooled EtOAc fractions were cleaned up by sequential partitioning with 2N NaOH and NaCl saturated water. The washed fractions are acidified with 0.1 N HCl and the acid layer removed and neutralized with 2N NaOH, NaCl, and additional EtOAc. The resulting EtOAc fraction is acidified (0.1 N HCl) and the acid layer is analyzed spectrophotometrically for thiabendazole.

For method validation, samples of pears, apples, apple juice, and dried apple pomace were fortified with thiabendazole. Fortification levels and method recoveries of thiabendazole are summarized in Table 1. The validated detection limits for the method are 0.2 for pears, 0.02 ppm for apples, 0.03 ppm for apple juice, and 0.5 ppm for dried apple pomace. Sample calculations and standard fluorescence spectra were provided.

CBRS has concluded that BNZ and 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 lab validation.

Table 1. Recoveries of thiabendazole from control samples fortified with thiabendazole.

Commodity	Fortification Level (ppm)	# of Samples	% Recovery
Pears	0.2	2	106, 117
	1.0	2	87, 88
	2.5	2	89, 91
Apples	0.02-10.0	22	75-97
Apple juice	0.03-1.0	16	84-100
Dried apple pomace	0.5	2	83, 88
	2.5	2	80, 84
	10.0	2	96, 100
	25	2	83, 83

Storage Stability Data

In conjunction with the submitted residue studies, Merck submitted data (1992; MRIDs 42515801 and 42515802) depicting the stability of thiabendazole in apples and processed apple commodities. Control samples of apple homogenate, juice, and dried pomace were fortified with thiabendazole at 0.1 ppm (apples and apple juice) and 1 ppm (dried apple pomace) and stored at -15 C for up to 273 days. Recoveries of thiabendazole from fortified control samples are shown in Table 2.

The submitted storage stability data indicate that thiabendazole per se is stable at -15 C for at least 273 days (9 months) in apples, apple juice, and dried apple pomace. However, CBRS has concluded that BNZ and conjugates are to be included in the tolerance expression. Therefore, the required residue and processing studies must be accompanied by supporting storage stability data for BNZ in addition to the parent thiabendazole.

Table 2. Stability of thiabendazole in apple commodities fortified with thiabendazole and stored at approximately -15 C.

	Fortified Control Samples[a]		
Commodity	# of Samples	Storage Interval (days)	% Recovery
Apples	3	0-273	82-94
Apple juice	3	0-273	80-98

Dried apple pomace	3	0-273	74-86

aControl samples of apples and apple juice were fortified with thiabendazole at 0.1 ppm, whereas control samples of dry pomace were fortified at 1 ppm. Recoveries are not corrected for method recovery.

Magnitude of the Residue in Plants

Pome fruits

A REFs search, dated 1/25/93, indicated that thiabendazole, formulated as a 42.5% and a 98.5% FlC, is currently registered for post-harvest use on apples and pears. The 42.5% FlC (EPA Reg. No. 618-75) is registered for a post-harvest dip application, before and after storing the fruit, at 600 ppm (0.48 lb ai/100 gal). Use directions for 98.5% FlC and WP labels include one post-harvest wax treatment at 1000 ppm (EPA Reg. Nos. 2972-50, 5202-26, and 43410-7).

Apples. A tolerance of 10 ppm has been established for residues of thiabendazole in or on apples [40 CFR 180.242(a)]. Merck Research Laboratories submitted data (1992; MRID 42515802) from five tests conducted in WA(2), NY(1), MI(1), and NC(1) depicting residues of thiabendazole in or on apples following a postharvest dip and a wax application of thiabendazole at 600 and 2000 ppm, respectively, corresponding to 1x and 2x the maximum registered application rates. Apples were dipped for 3 minutes within 4 hours following harvest (except MI, a 56-day interval), air dried, and placed in cold storage at 32-40 C. After 30 days of storage, thiabendazole was reapplied as a wax treatment. Samples were stored at approximately -15 C for 89-268 days prior to analysis. Residues of thiabendazole in or on apple samples were determined fluorometrically using Merck S.A.P. 500-A-011. Thiabendazole residues were 2.7-3.4 ppm in or on six apple samples following dip (1x) and wax (2x) applications of thiabendazole. Apparent residues of thiabendazole were <0.02 ppm (non-detectable) in or on five control samples.

These data indicate that thiabendazole residues per se in or on apples are not likely to exceed the established tolerance of 10 ppm for residues of thiabendazole in/on apples following a postharvest dip and wax application of thiabendazole at the maximum label rates. However, CBRS has concluded that BNZ and

conjugates are to be included in the tolerance expression. After adequate analytical methodology is developed that is capable of detecting BNZ and conjugates, residue data for BNZ must be submitted reflecting registered uses on apples. Additional data are required.

Pears. A tolerance of 10 ppm has been established for residues of thiabendazole in or on pears (40 CFR 180.242). Merck Research Laboratories submitted data (1992; MRID 42515802) from three tests conducted in CA(1), WA(1), and NY(1) depicting residues of thiabendazole in or on pears following a postharvest dip and a wax application of thiabendazole at 600 and 2000 ppm, respectively, corresponding to 1x and 2x the maximum registered application rates. Pears were dipped for 3 minutes within 2-19 hours following harvest, air dried, and placed in cold storage at 32-50 C. After 30 days of storage, thiabendazole was reapplied as a wax treatment. Samples were stored at approximately -15 C for 237-269 days prior to analysis. Residues of thiabendazole in or on pear samples were determined fluorometrically using Merck S.A.P. 500-A-011. Thiabendazole residues were 2.7-3.4 ppm in or on six pear samples following dip (1x) and wax (2x) applications of thiabendazole. Apparent residues of thiabendazole were <0.02 ppm (non-detectable) in or on five control samples.

These data indicate that thiabendazole residues per se are not likely to exceed the established tolerance of 10 ppm for residues of thiabendazole in or on pears following a postharvest dip and

wax application of thiabendazole at the maximum label rate. However, CBRS has concluded that BNZ and conjugates are to be included in the tolerance expression. After adequate analytical methodology is developed that is capable of detecting BNZ and conjugates, residue data for BNZ must be submitted reflecting registered uses on pears. Additional data are required.

Magnitude of the Residue in Processed Foods/Feeds

Apple Processed Commodities. A tolerance of 33 ppm has been established for residues of thiabendazole in or on processed dry apple pomace [40 CFR 186.5550(a)]. Merck Research Laboratories submitted data (1992; MRID 42515802) from a test conducted in NY depicting thiabendazole residues in or on whole apples, apple juice, and wet and dry apple pomace. Thiabendazole was applied as a postharvest dip application at 600 ppm and 30 days later as a wax application at 2000 ppm (1x the maximum registered rate for

the dip and 2x for the wax). Following the wax application, apples were stored at -15 C for one day prior to processing. A single bulk sample of apples was processed into apple juice, wet pomace, and dry pomace using a simulated commercial process. Thiabendazole residues in or on whole apples, apple juice, and dry pomace were determined using Merck method S.A.P. 500-A-011. Duplicate subsamples of whole apples, apple juice, wet pomace and dry pomace were analyzed. Residues of thiabendazole in or on whole apples, apple juice, wet pomace and dry pomace are shown in Table 3. Apparent residues of thiabendazole in or on control samples were: whole apples (<0.02 ppm), apple juice (<0.01 ppm), wet pomace (<0.03 ppm), and dry pomace (<0.1 ppm).

Data from the apple processing study indicate that residues of thiabendazole concentrated in wet pomace by 3.5x and in dry pomace by 11.6x the level of thiabendazole in or on whole apples. However, additional data are needed to determine the potential for concentration of BNZ. The appropriate level for a feed additive tolerance will be determined after (i) the newly defined tolerance level for apples is determined, and (ii) data are available to determine the potential for concentration of combined thiabendazole and BNZ residues.

Table 3. Thiabendazole residues in or on whole apples, apple juice, and dry and wet pomace resulting from postharvest applications of thiabendazole to apples.

Commodity	Residues (ppm)	Concentration factor (x)
Whole apples	3.9	--
Juice	1.1	--
Wet pomace	13.6	3.5
Dry pomace	45.1	11.6

aValues are the average of duplicate analyses.

References

Citations for the MRID documents referenced in this review are presented below. Submissions reviewed in this document are

indicated by shaded.type.

42515801..Norton,.J.;.Armstrong,.T..(1992).Determination.of.the Magnitude.of.the.Residues.of.the.Fungicide Thiabendazole.in.Pome.Fruit.(Pears).Treated.With.a.Dip and.Wax.Treatments:.Laboratory.Project.Study.#93104.. Unpublished.Study.prepared.by.Merck.Research Laboratories...532.p.

42515802..Norton,.J.;.Armstrong,.T..(1992).Determination.of.the Magnitude.of.the.Residues.of.the.Fungicide Thiabendazole.in.Pome.Fruit.(Apples).Treated.With.a Dip.and.Wax.Treatments:.Laboratory.Project.Study #93109...Unpublished.Study.prepared.by.Merck.Research Laboratories...585.p.

Agency Memoranda

CBRS No. 6781
Subject: Thiabendazole Post-Harvest Treatment Protocols; I.D. No. 60101.
From: C. Olinger
Dated: 7/11/90
MRID(s): None.

CBRS No. 8181
Subject: Thiabendazole: Time extension Request and Magnitude of Residue for Post-Harvest Treatments Inquiry.
From: C. Olinger
Dated: 7/16/91
MRID(s): None.

CBRS No. 8192
Subject: Thiabendazole Phase V Review. Metabolism Studies: Wheat, Soybean, and Sugar Beet.
From: L. Cheng
Dated: 3/11/92
MRID(s): 41872901, -02, and -03