7/30/93 -92

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

JUL 30 1993

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Thiabendazole, Reregistration. Magnitude of the Residue in Citrus and Citrus Processed Commodities (MRID No. 42568001).
CBRS No. 11216. DP Barcode No. D186592.

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Attached is a review of residue chemistry data for magnitude of the residue in citrus fruit and citrus processed commodities, submitted by registrant Merck and Company, Inc., in response to Phase 4 Review and as a completed study following a preliminary report of overtolerance residues in accordance with FIFRA 6(a)(2) guidelines. This information was reviewed by Acurex Corporation under supervision of CBRS, HED. The data assessment has undergone secondary review in the branch and has been revised to reflect branch policies.

Note to RD PM: A copy of the review is being provided to RD because of the potential for treatment at registered rates to result in residues in excess of the existing tolerance.

The review concluded that additional data are required before the residue study and the processing study can be considered acceptable. Even with the deficiencies identified, however, the available data indicate that treatment at registered rates may result in residues in excess of the existing tolerance for citrus fruit. The most straightforward resolution of the finding of

over-tolerance residues would be for registrant to propose new tolerances, toxicological considerations permitting, without waiting for additional residue data but using conservative assumptions to take into account the deficiencies identified in the available data.

If you need additional input please advise.

cc:Circ, Abbotts, RF, Thiabendazole List B File, SF, Acurex
RDI:FBSuhre:7/26/93:MSMetzger:7/26/93:EZager:7/29/93
H7509C:CBII-RS:JAbbotts:CM-2:Rm805A:305-6230:7/30/93
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THIABENDAZOLE
(Chemical Codes 060101 & 060102)
(CBRS No. 11216; DP Barcode D186592)

TASK 2B

Phase 5 - Reregistration Review
Residue Chemistry

May 25, 1993

Contract No. 68-DO-0142

Submitted to:

U.S. Environmental Protection Agency
Arlington, VA 22202

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THIABENDAZOLE

(Chemical Codes 060101 & 060102)

(CBRS No. 11216; DP Barcode D186592)

PHASE 5 - REREGISTRATION REVIEW RESIDUE CHEMISTRY

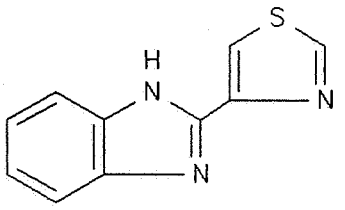
Task 2B

BACKGROUND

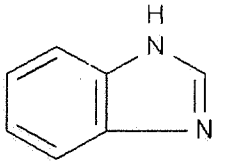
The Thiabendazole Phase 4 review dated 2/91 required data depicting residues of thiabendazole and its regulated metabolites in or on citrus fruit following postharvest treatments with thiabendazole as a dip followed by a wax application, both at concentrations of 5000 ppm. Data were also required depicting residues of thiabendazole and its regulated metabolites in citrus commodities processed from oranges and grapefruit bearing measurable weathered residues. CBRS tentatively approved a citrus postharvest protocol, provided that the specified application rates reflected a 1x maximum use (CBRS 6781, 7/11/90, C.L. Olinger), and also tentatively approved that the treated citrus samples be analyzed for residues of thiabendazole per se, pending the outcome of plant metabolism studies (CBRS 8181, 7/16/91, C.L. Olinger). Plant metabolism requirements were recently fulfilled, and the degradate benzimidazole (BNZ) and its conjugates were identified as additional residues of toxicological concern (CBRS 8192, 3/11/92, L. Cheng).

Merck & Co. Inc. (1992; MRID 42315701; reviewed by CBRS 10168, 7/27/92, C.L. Olinger) submitted preliminary (unaudited) residue data for citrus as 6(a)(2) because overtolerance residues were found, and indicated that a completed study would be forthcoming. The audited study (1992; MRID 42568001) has now been submitted, depicting residues of thiabendazole per se in or on citrus fruit and processed commodities. These data 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 citrus and processed citrus commodities.

The nature of the residue in plants and animals is adequately understood. The residues of concern in plants are thiabendazole, BNZ, and BNZ conjugates (CBRS 8192, 3/11/92, L. Cheng). The residues of concern in animals are thiabendazole, 5-OH thiabendazole (free and conjugates), and BNZ (Memo, 2/14/92, L. Cheng). 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. A method is available for determining residues of thiabendazole and 5-OH-thiabendazole in milk, and is listed in PAM, Vol. II, as Method D.



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 HED Metabolism Committee has concluded that the tolerance expression for animal commodities should include thiabendazole, 5-OH thiabendazole (free and conjugates), and BNZ (Memo, 2/14/92, L. Cheng).

U.S. tolerance and Codex MRLs (CXL) for residues of thiabendazole per se in or on citrus fruit are currently identical (10 ppm). The U.S. tolerance definition is also currently compatible with the corresponding Codex MRL. However, if the U.S. tolerance expression is expanded to include residues of BNZ and its conjugates, then the U.S. and Codex MRL definitions will no longer be compatible. In addition, the registrant has stated its intent to propose a higher tolerance for citrus fruit; if a higher tolerance is approved, then the U.S. tolerance and the Codex MRL will no longer be compatible.

CONCLUSIONS

1a. The submitted data indicate that method S.A.P. 500-C-042 is adequate for determining residues of thiabendazole per se in or on whole citrus fruits, and that method S.A.P. 500-C-043 is acceptable for determining residues of thiabendazole in or on citrus processed commodities.

1b. Data collection and tolerance enforcement methodology capable of quantifying BNZ and its conjugates must be developed. Methods proposed for enforcement must undergo independent laboratory validation prior to being submitted for EPA lab validation.

2a. The submitted storage stability data indicate that residues of thiabendazole per se are stable for at least 9 months in or on citrus fruit, oil, molasses, and peel/pulp stored at -26 °C.

2b. Adequate storage stability data have been submitted for residues of thiabendazole per se to support the current processing data.

2c. Storage stability data for residues of BNZ are required, reflecting the maximum storage intervals and storage conditions of treated samples.

3. In sequential treatments of citrus fruit post-harvest by dip and wax, the target rate for the dip represented approximately 1x the maximum registered rate, and the target rate for the wax application represented approximately 2.3x the maximum registered rate. Submitted data indicate that registered use may result in residues in excess of the current tolerance for thiabendazole per se (10 ppm) in or on citrus fruit. Registrant has stated the intent to propose a tolerance of 20 ppm.

4. Several potential deficiencies in the current study for post-harvest treatment of citrus have been identified which require further explanation. The registrant must submit:

i) the results of all pre- and post-test analyses of the test formulations (including dates of each analysis and identification of each formulation sample analyzed), an explanation of the decreased percentage ai found in returned formulation and summarized in the current submission (the level of ai in the returned samples was as low as 0.16x the expected level for maximum registered use), and a discussion of the possible impact on the field test results of the decreased percent ai;

ii) the results of all analyses of treated samples that were performed during the course of the study that are not included in the current submission. These data may be summarized in a tabular format, but should also include the assay tables for each analysis;

iii) an explanation of the correction mechanism (if any) applied to the residues or apparent residues of thiabendazole found in or on each treated or control sample reported in MRIDs 42315701 and 42568001; and

iv) a justification of why it was not necessary to analyze a fortified sample concurrently with each analytical set of treated and/or control samples to demonstrate adequate method recovery for all sample sets.

5. After adequate methodology is developed that is capable of detecting BNZ and conjugates, residue data are required depicting residues of BNZ and its conjugates in or on citrus fruit following treatments at 1x the maximum or intended label rates.

6a. After adequate methodology is developed that is capable of detecting BNZ and conjugates, residue data are required depicting residues of BNZ and its conjugates in or on citrus fruit and processed commodities following treatments at 1x the maximum or intended label rates, if detectable residues are found in or on the RAC, or at

exaggerated rates sufficient to produce measurable residues if nondetectable residues are found in or on the RAC at the 1x rate.

6b. Data submitted in MRID 42568001 indicate that residues of thiabendazole per se concentrated up to 1.6x in dried pulp, and 2.7x in oil. These concentration factors may change when all data have been submitted for the current study, and when residues of BNZ and its conjugates are taken into account. Data are needed determining the potential for concentration of BNZ and its conjugates in citrus processed commodities. Appropriate levels for food/feed additive tolerances will be determined after (i) all outstanding data for residues of thiabendazole, BNZ, and BNZ conjugates have been received, and (ii) an appropriate tolerance level for citrus fruits has been determined.

RECOMMENDATIONS

Registrant must explain whether all the deficiencies identified in Conclusions 3 and 4 could be resolved without a new citrus residue study. Additional data are required on residues in or on citrus fruit and processed commodities to resolve Conclusions 5, 6a, and 6b.

Even with the deficiencies identified above, available data indicate that treatment at registered rates may lead to residues which exceed the existing tolerance for citrus fruit of residues of parent thiabendazole only at 10 ppm. The data in the completed study therefore support the preliminary report under FIFRA 6(a)(2) guidelines of over-tolerance residues (CBRS 10168, 7/27/92, C.L. Olinger). The most straightforward resolution would be for registrant to propose new tolerances, toxicological considerations permitting, without waiting for additional residue data but using conservative assumptions to take into account the deficiencies identified in the available data. Because residues of parent thiabendazole concentrate in citrus processed commodities (Conclusion 6b), revised feed additive tolerances may also be necessary.

DETAILED CONSIDERATIONS

Reregistration Requirements

Phase 4 Review (2/21/91, C.L. Olinger) required data on the nature of the residue in plants, and residue data from field trials and processing studies in citrus. Data were required depicting residues of thiabendazole and regulated metabolites in or on citrus fruits. Thiabendazole must be applied post-harvest twice as a dip and a wax at a solution concentration of 5000 ppm for the dip and wax. Phase 4 Review referred to previous review of a protocol (DEB 6781, 7/11/90, C.L. Olinger) for these studies which approved the states for field trials: mandarin, Valencia and navel oranges in FL and navel and Valencia oranges, grapefruit, and lemons in CA. A processing study was required for oranges and grapefruit. The fruit bearing detectable residues of parent and regulated metabolites should be processed into wet and dry pulp, oil, molasses, and juice to determine residue concentration factors.

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A subsequent review concluded that pending review of metabolism studies, determination for parent thiabendazole only would be required when citrus and pome fruits were analyzed for magnitude of the residue from post-harvest treatment (CBRS 8181, 7/16/91, C.L. Olinger). Review of plant metabolism studies recommended that the residues of concern in plants were thiabendazole and benzimidazole (BNZ) and its conjugates; registrant was required to develop a method capable of measuring conjugates of BNZ (CBRS 8192, 3/11/92, L. Cheng). Residue data on apples and pears from post-harvest treatment have been submitted and reviewed; additional data on residues of BNZ and conjugates were required after adequate methodology has been developed (CBRS 10954, 4/15/93, R.B. Perfetti).

Residue Analytical Methods

Merck & Co. Inc. (1992; MRID 42568001) submitted analytical method descriptions for determining the residues of thiabendazole per se in or on citrus fruits and processed commodities. Thiabendazole residues were determined using Merck Standard Assay Procedures S.A.P. 500-C-042 (whole fruit) or S.A.P. 500-C-043 (processed fractions). These methods are modifications of Method I in PAM Vol. II, which has successfully undergone Agency validation. Briefly, residues are extracted into EtOAc, washed with 2N NaOH and NaCl saturated water, partitioned into an aqueous acidic phase (0.1 N HCl), and repartitioned into EtOAc using 2N NaOH, 2N NaOAc, and NaCl. The residues are then partitioned into an aqueous acidic phase (0.1 N HCl), and the acid layer is analyzed spectrofluorometrically for thiabendazole using an excitation wavelength of ~305 nm and an emission wavelength of ~360 nm.

For method validation, samples of grapefruit and grapefruit processed fractions were fortified with thiabendazole; fortification levels and method recoveries of thiabendazole are shown in Table 1. The registrant reported that the limits of quantitation (LOQ) are 0.04 ppm (whole fruit), 0.2 ppm (oil), 0.05 ppm (juice), 0.2 ppm (molasses), and 0.5 ppm (dry pulp). Sample calculations and standard fluorescence spectra were provided. As noted in Table 1, recoveries >120% were obtained from whole fruit samples fortified with thiabendazole at levels <0.2 ppm; for purposes of this review, 0.2 ppm is taken to be the demonstrated LOQ for whole citrus fruit.

Concurrent method recoveries from storage stability analyses were 78-101% from three grapefruit samples fortified at 0.5 ppm with thiabendazole, and were 86-112% from three samples each of grapefruit oil, molasses, and dry peel/pulp fortified at 2 ppm with thiabendazole (Table 2).

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Table 1. Method validation recoveries from citrus fruit and processed fractions fortified with thiabendazole.

Matrix	Method: S.A.P. 500-C-	Fortification level (ppm)	% Recovery[a]	Apparent residues in or on control samples (No. of samples)	LOQ for matrix
Whole grapefruit	-042	0.04	132, 136[b]	<0.04-0.04 (6)	0.2[c]
		0.1	127, 127[b]		
		0.2	106, 96		
		0.4	91, 97		
		0.67	101, 104		
		1	86, 92		
		2	96, 99		
		4	88, 91		
		10	87, 89		
		0.04	102, 110		
		0.1	103, 100		
oil	-043	0.2	108, 106	<0.2 (2)	0.2
		0.8	94, 77		
		4	106, 99		
		10	94, 103		
juice	-043	0.05	96, 94	<0.05 (2)	0.05
		0.1	91, 96		
		0.33	99, 95		
molasses	-043	0.1	86, 93	<0.2 (2)	0.2
		0.2	91, 91		
		0.5	88, 88		
		0.8	71, 71		
		2	80, 91		
		5	80, 90		
dry pulp	-043	0.1	89, 107	<0.5 (4)	0.5
		0.25	110, 124		
		0.5	85, 108		
		1	82, 87		
		2.5	91, 91		
		10	100, 95		
		25	92, 85		

[a]Recoveries from duplicate injections of a single control sample fortified at each level. [b]The registrant speculated that these samples might have been contaminated. [c]The registrant reported the limit of quantitation (LOQ) for grapefruit to be 0.04 ppm; however, for purposes of this review, the demonstrated LOQ is taken to be 0.2 ppm, the lowest fortification level for which acceptable recoveries were obtained.

Conclusion 1a: The submitted data indicate that method S.A.P. 500-C-042 is adequate for determining residues of thiabendazole per se in or on whole citrus fruits, and that method S.A.P. 500-C-043 is acceptable for determining residues of thiabendazole in or on citrus processed commodities.

Conclusion 1b: Data collection and tolerance enforcement methodology capable of quantifying BNZ and its conjugates must be developed. Methods proposed for enforcement must undergo independent laboratory validation prior to being submitted for EPA lab validation.

Storage Stability Data

Merck & Co. Inc. (1992; MRID 42568001) submitted data depicting the storage stability of thiabendazole in or on citrus and citrus processed commodities. Control samples of grapefruit and grapefruit oil, molasses, and peel/pulp were fortified with thiabendazole at 0.5 ppm (whole fruit) and 2 ppm (oil, molasses, and peel/pulp) and stored at -26 °C for up to 9 months (273 days). Recoveries of thiabendazole from stored and freshly fortified samples are shown in Table 2.

These data indicate that residues of thiabendazole per se are stable for at least 9 months in or on citrus fruit, oil, molasses, and peel/pulp stored at -26 °C. For the current residue studies, citrus fruits were stored at 4°C for 5-7 days prior to processing, and the processed samples were stored frozen for 144-155 days from the time of processing until analysis. Whole fruit samples were stored frozen for 47-392 days from treatment until analysis. Adequate storage stability data have been submitted for residues of thiabendazole per se to support the current processing data; however, additional data are required for residues of BNZ and BNZ conjugates.

Conclusion 2a: The submitted storage stability data indicate that residues of thiabendazole per se are stable for at least 9 months in or on citrus fruit, oil, molasses, and peel/pulp stored at -26 °C.

Conclusion 2b: Adequate storage stability data have been submitted for residues of thiabendazole per se to support the current processing data.

Conclusion 2c: Storage stability data for residues of BNZ are required, reflecting the maximum storage intervals and storage conditions of treated samples.

Table 2. Storage stability of thiabendazole per se in or on whole citrus fruit and processed commodities.

Commodity	Fortification level (ppm)	Storage interval (months)	% Recoveries[a]	
			Stored samples	Fresh fortification
Whole grapefruit	0.5	0	78, 89	78, 81
		3	91, 95	94, 100
		9	91, 100	98, 101
oil	2	0	101, 95	91, 89
		3	96, 95	90, 105
		9	100, 108	106, 109
molasses	2	0	89, 95	88, 95
		3	86, 90	90, 85
		9	87, 88	92, 86
dry peel/pulp	2	0	96, 96	94, 98
		3	98, 102	102, 112
		9	81, 90	88, 94

[a]Recoveries from duplicate injections of one stored and one freshly fortified sample per interval per commodity, corrected for apparent residues in or on control samples. Apparent residues in or on control samples were nondetectable (< matrix LOQ) for all controls (one per commodity per storage interval).

Magnitude of the Residue in Plants

Citrus fruits. A tolerance of 10 ppm has been established for residues of thiabendazole in or on citrus [40 CFR §180.242(a)]. CBRS has recommended that the tolerance definition for plants be expanded to include residues of BNZ and its conjugates.

A LUIS report dated 1/22/91 and a REFS search dated 3/30/93 identified 20 end-use products currently registered to 6 companies for postharvest uses on citrus [4 WP formulations (wax, spray, flood, and drench applications); 5 FlC formulations (wax, spray, flood, and dip applications); 8 RTU/L formulations (wax applications), and 3 SC/L formulations (wax, spray, flood, and dip applications)]. Merck & Co. Inc. currently has no end-use products registered for postharvest application to citrus, but manufactures the only thiabendazole FI (98.5%; EPA Reg. No. 618-67). Current end-use labels specify a maximum concentration of thiabendazole in treatment solutions at 5000 ppm delivered at a rate of application of 1 gallon per 8-10,000 pounds of citrus fruit or at an unspecified rate/duration (CBRS 7776, 5/9/91, B. Cropp-Kohlligian). The registrant's protocol specified (CBRS 6781, 7/11/90, C. Olinger), and the current submission reflects, sequential dip and wax applications at rates of 5000 ppm solution (dip) and 1 gal 5000 ppm wax suspension/3500 lb fruit.

Merck & Co. Inc. (1992; MRID 42568001) submitted data from 12 tests conducted in CA(4) and FL(8) depicting the residues of thiabendazole per se in or on citrus fruit (grapefruit, lemons, and oranges) following postharvest treatments. For eight tests, freshly harvested fruit were dipped for 3 minutes in an approximately 5000 ppm aqueous solution [prepared using a 5% FlC formulation (EPA Reg. No. 8764-42)], and were air dried. The same (7 tests) or the next day (5 tests) an approximately 5000 ppm aqueous wax suspension [prepared by adding 0.695 oz ai (98.5% FI; EPA Reg. No. 618-67) to 1 gal wax] was then misted or dripped onto the fruit at a rate of 1 gal wax per 3500 lbs of fruit, using commercial equipment. The registrant stated that these were the target rates, and implied that these rates are being supported as the intended 1x maximum; they are 1x the current maximum dip application rate, and approximately 2.3x the current maximum wax application rate (1 gal 5000 ppm suspension/8000 lb fruit). Four FL tests were repeated due to erroneous wax applications at 1.4-3.4 gal 5000 ppm suspension/3500 lb fruit. We note that the registrant summarized application rates in terms of ppm alone, reporting that the wax applications were 7,050-17,100 ppm for the erroneous tests. However, the field cooperators' reports show that the wax suspensions were prepared at approximately the target rate of 5000 ppm, and that it was gal/lb fruit that varied. Data from all 12 tests are presented here; the higher wax application rates did not result in higher thiabendazole residue values. A composite sample from each test was frozen following the wax treatment and stored at approximately -26 °C for 47-392 days prior to analysis using method S.A.P. 500-C-042.

Residues of thiabendazole per se found in or on whole grapefruit, lemons, and oranges are shown in Table 3. Overtolerance residues of 10.35-17.06 ppm were found in or on oranges or grapefruit from three of the FL tests receiving the target dip and wax applications, and overtolerance residues of 11.80, 11.97 ppm (duplicate injections) were found in or on a grapefruit sample from one FL test that received an elevated wax application (1.4 gal/3500 lb fruit). Residues were 1.22-9.55 ppm in or on the grapefruit, lemons, or oranges from the remaining eight tests. Apparent residues of thiabendazole were not detected at levels above the matrix LOQ (0.2 ppm) in or on the 12 control samples.

Multiple analyses were conducted for several samples. We note that the unaudited data table (MRID 42315701, reviewed by CBRS 10168, 7/27/92, 7/27/92)1992) reported residues for several sample analyses that were not reported in the current submission (MRID 42568001), and that several sample analyses were currently reported that did not appear on the previous submission. For example, MRID 42315701 included an analysis of sample number 640 (FL) that showed residues of 28.56 and 5.37 ppm from duplicate injections, with the comment that this sample was an outlier. This analysis was not included in the current submission. All relevant data should be submitted so that the Agency may draw its own conclusions.

We note that certain discrepancies between residue levels reported in the unaudited data table (CBRS 10168, 7/27/92, C.L. Olinger, MRID 42315701) and the residue levels currently reported for the same sample analyses indicate that some correction factor was applied to some analytical results. However, neither the unaudited data table nor the current submission reported what (if any) residue correction mechanism was employed.

Table 3. Residues of thiabendazole per se in or on citrus fruit following postharvest dip and wax treatments.

Test number (state)	Commodity (type)	Application method[a] and rate		Treated sample number	Residues of thiabendazole per se (ppm)[c]	Treated sample storage interval (days)
		Dip (ppm)	Wax (gal/3500 lb fruit)[b]		Treated samples[d]	
3049 (CA)	Oranges (Navel)	5000	1	661	1.78, 1.76	202
3050 (CA)	Oranges (Valencia)	5000	1	662	1.22, 1.22	76
3051 (CA)	Grapefruit (Pink)	4994	1	157	2.85, 2.87	185
3052 (CA)	Lemons (Lisbon)	4994	1	65	5.06, 5.39	187
3053 (FL)[e]	Oranges (Mandarin)	5000	3.4	638	3.33, 2.99	153
				638	3.06, 3.06	154
				638	3.22, 3.41	260
3054 (FL)[e]	Oranges (Navel)	5000	1.9	640	4.89, 4.96	154
				640	6.75, 6.41	260
3055 (FL)[e]	Oranges (Valencia)	5000	1.5	642	5.19, 5.06	47
				642	5.44, 5.78	153
3056 (FL)[e]	Grapefruit (Marsh)	5000	1.4	143	6.17, 6.80	161
				143	5.93, 5.99	53
				143	6.46, 6.36	54
				167	9.95, 9.74	370
				167	11.97, 11.80	372
				167	9.04, 9.68	392
				167	9.28, 9.78	377
				167	9.15, 8.91	377

Continued

Table 3. Continued

Test number (state)	Commodity (type)	Application method[a] and rate		Treated sample number	Residues of thiabendazole per se (ppm)[c]	Treated sample storage interval (days)
		Dip (ppm)	Wax (gal/3500 lb fruit)[b]		Treated samples[d]	
3071 (FL)[e]	Oranges (Valencia)	5000	1	664	9.07, 9.07	302
				664	6.80, 7.07	307
				664	8.15, 8.53	307
				664	8.91, 9.55	322
3072 (FL)[e]	Grapefruit (Marsh)	5000	1	169	6.55, 6.55	300
				169	10.35, 9.83	302
				169	6.99, 7.21	307
				169	7.36, 7.78	307
3073 (FL)[e]	Oranges (Navel)	5000	1	666	14.51, 14.87	63
				666	17.06, 16.56	68
				666	12.05, 12.30	68
				666	15.97, 16.36	83
3074 (FL)[e]	Oranges (Mandarin)	5000	1	668	10.69, 10.86	63

[a]Whole fruits dipped for 3 minutes, followed the same or the next day by a mist or drip application of wax. [b]Gallons of approximately 5000 ppm ai wax suspension [0.695 oz ai (20 gm of 98.5% FI formulation)/gal wax] applied per 3500 lb fruit; target rate was 1 gal/3500 lb fruit. [c]Residue values uncorrected for apparent residues in or on controls or for concurrent method recoveries. No data were reported concerning concurrent method recovery samples. [d]Residue values are individually shown for duplicate injections of each treated sample. [e]FL tests 3053, 3054, 3055, and 3056 were repeated to generate residue data reflecting 1x treatment.

No data were reported for method recoveries from spiked samples run concurrently with treated and/or control samples from the field or processing tests. In addition, residue sample analytical sets did not consistently include both control and treated samples. The registrant is advised that all future data submissions should include treated, control, and concurrent method recovery samples in all residue analytical sample sets. Data should be reported uncorrected, and may be accompanied by data corrected for apparent residues in or on control samples and for same-day recovery, provided the correction factor is clearly explained and consistently applied.

The registrant also reported summary data for analyses of the 5% FlC formulation performed prior to shipment to the field and of the unused product returned. The average pre-test results showed thiabendazole at 4.8% ai in the FlC, while the three post-test results reported showed thiabendazole at 2%, 1.6%, and 0.8%. The registrant must explain this discrepancy and discuss its impact on the study.

Geographic representation is adequate. The test states of FL(84%) and CA(15%) accounted for approximately 99% of the orange, 95% of the grapefruit, and 78% of the lemon production in the U.S. in 1990-91 (Agricultural Statistics 1991, p. 189).

Residues of thiabendazole per se in or on citrus exceeded the established 10 ppm tolerance for in or on oranges and grapefruit following a postharvest dip and sequential wax application of thiabendazole at the target rates of 5000 ppm for the dip and 1 gal 5000 ppm suspension/3500 lb fruit for the wax. The registrant has stated the intent to propose an increased tolerance of 20 ppm for citrus fruits.

Conclusion 3: In sequential treatments of citrus fruit post-harvest by dip and wax, the target rate for the dip represented approximately 1x the maximum registered rate, and the target rate for the wax application represented approximately 2.3x the maximum registered rate. Submitted data indicate that registered use may result in residues in excess of the current tolerance for thiabendazole per se (10 ppm) in or on citrus fruit. Registrant has stated the intent to propose a tolerance of 20 ppm.

Conclusion 4: Several potential deficiencies in the current study for post-harvest treatment of citrus have been identified which require further explanation. The registrant must submit:
i) the results of all pre- and post-test analyses of the test formulations (including dates of each analysis and identification of each formulation sample analyzed), an explanation of the decreased percentage ai found in returned formulation and summarized in the current submission (the level of ai in the returned samples was as low as 0.16x the expected level for maximum registered use), and a discussion of the possible impact on the field test results of the decreased percent ai;
ii) the results of all analyses of treated samples that were performed during the course of the study that are not included in the current submission. These data may be summarized in a tabular format, but should also include the assay tables for each analysis;
iii) an explanation of the correction mechanism (if any) applied to the residues or apparent residues of thiabendazole found in or on each treated or control sample reported in MRIDs 42315701 and 42568001; and

iv) a justification of why it was not necessary to analyze a fortified sample concurrently with each analytical set of treated and/or control samples to demonstrate adequate method recovery for all sample sets.

Conclusion 5: After adequate methodology is developed that is capable of detecting BNZ and conjugates, residue data are required depicting residues of BNZ and its conjugates in or on citrus fruit following treatments at 1x the maximum or intended label rates.

Recommendations: Registrant must explain whether all the deficiencies identified in Conclusions 3 and 4 could be resolved without a new citrus residue study. Additional data are required on residues in or on citrus fruit to resolve Conclusion 5.

Even with the deficiencies identified above, available data indicate that treatment at registered rates may lead to residues which exceed the existing tolerance for citrus fruit of residues of parent thiabendazole only at 10 ppm. The data in the completed study therefore support the preliminary report under FIFRA 6(a)(2) guidelines of over-tolerance residues (CBRS 10168, 7/27/92, C.L. Olinger). The most straightforward solution would be for registrant to propose new tolerances, toxicological considerations permitting, without waiting for additional residue data but using conservative assumptions to address the deficiencies identified in the available data. Because residues of parent thiabendazole concentrate in citrus processed commodities (see below), revised feed additive tolerances may also be necessary.

Magnitude of the Residue in Processed Foods/Feeds

Citrus Processed Commodities. Tolerances of 20 ppm and 35 ppm have been established for residues of thiabendazole per se in or on citrus molasses and dried citrus pulp, respectively [40 CFR §186.5550(a)]. CBRS has recommended that the tolerance definition in plants be expanded to included residues of BNZ and its conjugates.

Merck & Co. Inc. submitted data (1992; MRID 42568001) from 2 tests conducted in FL depicting residues of thiabendazole per se in or on oranges and grapefruit and their processed commodities. Thiabendazole was applied as a postharvest dip (5000 ppm) and allowed to dry, and a second application was made as an aqueous wax (1.4-1.5 gal 5000 ppm suspension/3500 lb fruit) using commercial equipment. These rates are 1x the current maximum rate for the dip and 3.2-3.4x the current maximum rate for the wax. Following the wax application, a composite sample of fruits from each test was stored at 4 °C for 5-7 days prior to processing into juice, wet and dry pulp, oil, and molasses using simulated commercial processes. Processed samples were stored at approximately -26 °C for 144-155 days prior to analysis. Residues of thiabendazole per se in or on whole citrus, citrus juice, wet and dry pulp, oil, and molasses were determined using the methods S.A.P. 500-C-042 (whole fruit) and S.A.P. 500-C-043 (processed fractions).

Average residues of thiabendazole found in or on treated and control fractions are shown in Table 4. The registrant stated that the control and treated whole washed fruit samples from test 3057 were inverted; the sample labeled as treated bore nondetectable residues (<0.2 ppm), whereas the sample labeled as control bore average residues of 1.1 ppm. Residues were nondetectable (< matrix LOQ) in or on the remaining whole fruit, juice, and pulp control samples, and were <0.2-0.32 ppm in or on the molasses and <0.2-0.58 ppm in or on the oil control samples of grapefruit and oranges.

Concentration factors for residues of thiabendazole per se are also calculated in Table 4. The grapefruit and orange treated RAC samples analyzed for the processing portion of the study, and used by the registrant to calculate concentration factors, were washed as part of the processing procedure. Using washed RAC samples to calculate concentration factors for processed fractions exaggerates the residue concentration factors. The RAC samples used by the reviewer to calculate concentration factors in Table 4 are those that were analyzed for the magnitude of residue portion of the submission, from the tests that yielded the processing subsamples.

Conclusion 6a: After adequate methodology is developed that is capable of detecting BNZ and conjugates, residue data are required depicting residues of BNZ and its conjugates in or on citrus fruit and processed commodities following treatments at 1x the maximum or intended label rates, if detectable residues are found in or on the RAC, or at exaggerated rates sufficient to produce measurable residues if nondetectable residues are found in or on the RAC at the 1x rate.

Conclusion 6b: Data submitted in MRID 42568001 indicate that residues of thiabendazole per se concentrated up to 1.6x in dried pulp, and 2.7x in oil. These concentration factors may change when all data have been submitted for the current study, and when residues of BNZ and its conjugates are taken into account. Data are needed determining the potential for concentration of BNZ and its conjugates in citrus processed commodities. Appropriate levels for food/feed additive tolerances will be determined after (i) all outstanding data for residues of thiabendazole, BNZ, and BNZ conjugates have been received, and (ii) an appropriate tolerance level for citrus fruits has been determined.

Recommendation: Additional data are required on residues in citrus processed commodities to resolve Conclusions 6a and 6b.

Table 4. Concentration of residues of thiabendazole per se in or on citrus processed commodities following postharvest dip and wax treatments

Test number	Commodity	Application method and rate[a]		Treated sample number	Residues of thiabendazole per se (average ppm)[c]		Preliminary concentration factor	Treated sample storage interval (days)[e]
		Dip (ppm)	Wax[b] (gal/3500 lb fruit)		Treated samples[d] (No. of samples)	Control samples (No. of samples)		
3055 (RAC) and 3057 (processing)	Oranges (RAC sample)[f]	5000	1.5	642	5.37 (2)	<0.2 (3)	--	47, 153
	Oranges (washed)			654	1.1[g] (2)	<0.2[g] (3)	--	148, 365
	Orange juice			649	0.07 (1)	<0.05 (4)	--	147
	Orange molasses			650	5.33 (1)	<0.2-0.32 (4)	1x	148
	Orange oil			651	14.23 (1)	<0.2-0.58 (2)	2.7x	148
	Orange finishers pulp			652	0.16 (1)	<0.5 (4)	--	147
	Orange dry pulp			653	8.65 (1)	<0.5 (2)	1.6x	148
3056 (RAC) and 3058 (processing)	Grapefruit (RAC sample)[f]	5000	1.4	143, 167	8.56 (8)	<0.2 (2)	--	53-392
	Grapefruit (washed)			144	1.56 (1)	<0.2 (3)	--	154
	Grapefruit juice			145	0.06 (1)	<0.05 (3)	--	144
	Grapefruit molasses			146	9.15 (1)	<0.2-0.21 (3)	1.1x	154
	Grapefruit oil			147	14.19 (2)	<0.2-0.22 (2)	1.7x	154
	Grapefruit finishers pulp			148	0.15 (2)	<0.5 (3)	--	147, 155
	Grapefruit dry pulp			149	12.46 (1)	<0.5 (2)	1.5x	154

[a]Whole fruits dipped for 3 minutes, followed the same or the next day by a mist or drip application of wax. [b]Gallons of approximately 5000 ppm ai wax suspension (0.695 oz ai/gal wax) applied per 3500 lb fruit; target rate was 1 gal/3500 lb fruit. [c]Average residue values uncorrected for apparent residues in or on controls or for concurrent method recoveries. No data were reported concerning concurrent method recovery samples. [d]Separate extractions of a sample from a given test site are counted here as separate samples. [e]Days from treatment (RAC samples) or days from processing until analysis. [f]Orange and grapefruit RAC samples are those reported in Table 3 for test numbers 3055 and 3056, respectively. [g]Registrant reported that the treated and control samples were inverted; residues were found in or on the sample designated as the control, and were nondetectable (<0.2 ppm) in or on the sample designated as treated.

References

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

42315701 Sheehy, P. (1992) Letter Sent to OPP dated May 5, 1992: Thiabendazole Residue Data--Citrus [Unaudited interim residue data]. Prepared by Merck, Sharpe & Dohme. 5 p.

42568001 Norton, J.; Armstrong, T. (1992) Determination of the Magnitude of the Residues of the Fungicide Thiabendazole in Citrus Treated with a Dip and Wax Treatment: Lab Project Number: 93064: 001-90-3049R: SARS-90-CA-34. Unpublished study prepared by Merck Research Labs. 9 volumes, 1959 p.

Agency Memoranda

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

CBRS No. 7776
Subject: Thiabendazole Post Harvest use on Citrus. Amended registration for Decco Salt No. 19.
From: B. Cropp-Kohlligian
To: S. Lewis
Dated: 5/9/91
MRID(s): none

CBRS No. 8181
Subject: Thiabendazole: Time Extension Request and Magnitude of Residue for Post-Harvest Treatments Inquiry.
From: C. Olinger
To: F. Rubis
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
To: F. Rubis
Dated: 3/11/92
MRID(s): 41872901, -02, and -03

CBRS Nos. 8930, 8719
Subject: Thiabendazole. Phase V Review. Goat and Poultry Metabolism Studies.
From: L. Cheng
To: F. Rubis
Dated: 3/2/92
MRID(s): 42057901, 42011701

CBRS No. None
Subject: Thiabendazole Livestock (Goat and Poultry) Metabolism. The Metabolism Committee Meeting Held on February 12, 1992.
From: L. Cheng
To: The Metabolism Committee, HED
Dated: 2/14/92
MRID(s): None

CBRS No. 10954
Subject: Response to the Thiabendazole Phase IV Review: Residue Chemistry Data.
From: R.B. Perfetti
To: F. Rubis
Dated: 4/15/93
MRID(s): 42515801, 42515802