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7F3553

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

JUL 29 1988

CONFIDENTIAL

Memorandum:

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#7F3553/FAP#7H5541. Thiabendazole in/on Stored Corn Grain. Evaluation of Analytical Method and Residue Data. (MRID#'s 402717-02, -05, -06, and -07, RCB#'s 2777 and 2778).

FROM: Jerry B. Stokes, Chemist
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THRU: Charles L. Trichilo, Ph. D, Chief
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TO: Lois Rossi, PM-21
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Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

A cover letter dated July 15, 1987 from Merck Co., Inc. proposes that 1) a tolerance be established for the residues of the fungicide 2-(4-thiazolyl)benzimidazole (thiabendazole) in/on corn grain at 20 ppm, 2) the established tolerance for thiabendazole in/on grapes at 10 ppm be cancelled, 3) feed additive tolerances be established for the residues of thiabendazole in/on corn bran at 125 ppm, in/on corn fines at 40 ppm, in/on corn germ at 30 ppm, and in soapstock at 25 ppm, and 4) the established feed additive tolerance in/on processed grape pomace (dry or wet) at 150 ppm be cancelled.

Tolerances are established for residues of thiabendazole in/on various r.a.c.'s ranging from 0.02 to 40.0 ppm (40 CFR 180.242(a)). Tolerances are established for the combined residues of thiabendazole and its metabolite, 5-hydroxythiabendazole in livestock and poultry meat, fat, and meat byproducts, and eggs at 0.1 ppm and in milk at 0.4 ppm (40 CFR 180.242(b)). Feed additive tolerances are established for thiabendazole in various processed feeds ranging from 3.5 to 150 ppm (40 CFR 186.5550). In regards to animal drug use,

tolerances are established at 0.1 ppm for negligible residues of thiabendazole in uncooked edible tissues of cattle, goats, sheep, pheasants, and swine, and at 0.05 ppm for negligible residues in milk (21 CFR 556.730).

Summary of deficiencies:

1. A revised Section B should be submitted for clarification of label directions.

2. Residue data are needed for corn grain dust for the proposed use.

3. Residue data are needed for the wet milling process of corn grain.

4. A revised Section F should be submitted for:

   a. Proposed tolerance for corn, grain (post-H), should be increased from 20 ppm to 25 ppm for the proposed use.
   b. Feed and/or food additive tolerances will be needed for milled corn products and corn bran for the proposed use.
   c. Tolerances for cattle, goat, hogs, horses, and sheep meat byproducts, liver, and kidney, and for poultry kidney should be changed to cover the proposed use.

5. A revised Section F which deletes a revocation request for grape tolerances should be submitted if there are no other Agency data requirements and if it is the desire of the petitioner to retain the established tolerances.

6. An inert in the MERTECT-340F formulation must be cleared under 40 CFR 180.1001(c).

Conclusions:

1a. The residue of regulatory concern in/on plants for this proposed use is thiabendazole (TBZ).

1b. The nature of the residue in livestock is understood. The terminal residues of regulatory concern are TBZ and its metabolite 5-hydroxythiabendazole (5-OH-TBZ).

2a. An analytical method is available for enforcement of the proposed tolerance on corn grain.

2b. Methods for analyses of TBZ and 5-OH-TBZ in animal tissues as submitted in this petition are adequate, but methodologies are not yet recorded in PAM II methods.

2c. A multiresidue method is available for TBZ.

3. The proposed tolerance of 20 ppm for residues of TBZ may not be adequate to cover estimated residues from this post-harvest use on freshly harvested corn grain. Treatment and sampling procedures may lead to over tolerance residues for properly dosed corn grain. The tolerance request should be raised to 25 ppm for corn, grain (post-H). A revised Section F should be submitted.

4. The label must state the maximum/minimum spray volume, clarify what a "sufficient carrier" is, and place a label restriction that the pesticide can only be applied to freshly harvested corn grain which is destined for low temperature drying and storage. A revised Section B should be submitted.

5. The petitioner needs to submit residue data for corn grain dust which reflects the proposed use.

6a. Residue data are needed for the wet milling process for corn grain. The need for any additions and/or changes in the proposed feed and/or food additive tolerances, and subsequently in the established tolerances for meat, fat, meat byproducts, milk, and eggs, will be assessed after the wet milling processing data has been submitted and reviewed.

6b. Depending on the results of the wet milling processing study, and based on the residue data, if and when a thiabendazole tolerance is established for corn, grain (post-H), then feed additive tolerances should be established at these tentative levels as follows:

corn, milled fractions (exc bran and soapstock) (post-H)	40 ppm
corn bran (post-H)	145 ppm

A revised Section F should be submitted.

6c. Depending on the results of the wet milling processing study, and based on this data, if and when a thiabendazole tolerance is established for corn, grain (post-H), then food additive tolerances should be established at these tentative levels as follows:

corn, milled fractions (exc bran) (post-H)	40 ppm
corn bran (post-H)	145 ppm

A revised Section F should be submitted.

7. After reviewing the data submitted in this petition, revocation of the established tolerances of 10 ppm for the r.a.c., grapes, and 150 ppm for grape pomace (wet or dry) are not necessary to satisfy any Residue Chemistry Branch concerns. A revised Section F which deletes this revocation request should be submitted if there are no other Agency data requirements and if it is the desire of the petitioner to retain the established tolerances.

8. The established tolerance of 0.4 ppm is adequate to cover estimated combined secondary residues of TBZ and its metabolite 5-OH-TBZ in milk from the proposed use.

9a. The established tolerances of 0.1 ppm for eggs, poultry meat, meat byproducts (exc kidney) and fat are adequate to cover

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estimated secondary residues of TBZ and its metabolite, 5-OH-TBZ, from the proposed use. A tolerance should be established for poultry kidney at 0.2 ppm, and poultry meat byproducts should be changed as follows:

poultry meat byproducts (exc kidney)	0.1 ppm

A revised Section F should be submitted.

9b. The established tolerances of 0.1 ppm for cattle, goat, hogs, horses, and sheep meat and fat are adequate to cover estimated secondary residues of TBZ and its metabolite, 5-OH-TBZ, from the proposed use.

9c. For the proposed use the established tolerances of 0.1 ppm for secondary residues of TBZ and its metabolite, 5-OH-TBZ, in cattle, goat, hogs, horses, and sheep meat byproducts should be changed as follows:

meat byproducts (exc. liver, kidney)	0.1 ppm
liver	0.4 ppm
kidney	0.4 ppm

Fat and meat tolerances remain 0.1 ppm. A revised Section F should be submitted.

10. The petitioner should request clearance for one inert in the MERTECT-340F formulation (See Attachment 1: Confidential Appendix).

Recommendations:

RCB recommends against the proposed tolerances for the residues of thiabendazole in/on stored corn grain because of the deficiencies 3, 4, 5, 6a, 6b, 6c, 9a, and 9c. Revocation of the established tolerances of 10 ppm for r.a.c. of grapes and of 150 ppm for grape pomace (wet or dry)(40 CFR 180.242(a) and 40 CFR 186.5550, respectively) are not necessary to satisfy any Residue Chemistry Branch concerns.

Note to PM: One inert in the Mertect-340F formulation should be cleared under 40 CFR 180.1001(c); please see Attachment 1: Confidential Appendix.

Detailed Considerations:

Manufacture and Formulation

The basic manufacturing process of the a.i. technical grade thiabendazole is described in company letter to Agency (See PP#7F3553/7H5541, letter of R. R. Buck, 2/15/77). The technical grade a.i. is 98.5% (min) pure. (See Confidential Appendix.)

The proposed formulation is MERTECT 340-F (3.8 lb a.i./gal) which contains 42.28% a.i. and 57.72% inerts. The inerts have been cleared under 40 CFR 180.1001(c) and 21 CFR 74.1705. The

petitioner should request clearance for an inert under 40 CFR 180.1001(c) (See Confidential Appendix).

Proposed Use

This fungicide is applied at a rate of 0.03 fl oz (0.014 oz a.i.) during low temperature drying and long term grain storage. Since a standard bushel of corn grain weighs 56 lbs and corn grain contains 15 to 20 percent moisture content after drying, then the final treatment concentration is ca 20 ppm on a dry weight basis.

The petitioner has stated that MERTECT-340F should be applied in a sufficient carrier for coverage. Neither a concentration of the application mix nor a total spray volume are recommended by the petitioner other than an application limit of 0.03 fl oz (0.014 oz a.i.)/bushel. The submitted residue data in this petition used application volumes of 3.0 and 4.0 fl oz/ bushel, and one trial at 3.8 to 5.9 fl oz/bushel. The petitioner should include a minimum application volume in a revised Section B.

To prevent multiple applications, and possible over-tolerance situations, the petitioner should add label restriction that pesticide can only be applied to freshly harvested corn grain which is destined for low temperature drying and storage; this pesticide can not be applied to stored grain already dried.

Nature of the Residue

In plants: The fate of thiobendazole from post-harvest use on treated citrus (See PP#8F0724) and apples, crabapples, and pears (PP#1F1031) was discussed previously with PP#1031 (See memo of 12/29/70, E. Gunderson). With citrus, adsorption into the interior of the fruit during a 4-week storage is inconsequential (<0.01 ug/g). The thiobendazole is stable and practically completely recovered as parent after 4 weeks; thiabendazole residues remained predominantly in the fruit peel. Treatment of potato seed tubers with

^{14}C-thiobendazole showed no metabolism of pesticide when potatoes were stored for 3 months (See PP#5F1537, Acc#118957). With cotton and soybean seedlings using ^{14}C-thiabendazole, the parent compound is absorbed and translocated intact; thiabendazole is not metabolized or bound by plant constituents (See PP#2F2603, M.Bradley, 2/8/82). Thiabendazole is the only residue stated in the tolerance expression [40 CFR 180.242(a)] for raw plant agricultural commodities.

In animals: The metabolic fate of thiobendazole in ruminants has been discussed previously (See PP#80674, 3/8/68, W. Brodee). Submitted articles entitled "Absorption, Metabolism, and Excretion of Thiabendazole in Man and Laboratory Animals" [Tox. and Appl. Pharm. 9, 31 (1966), See PP2F1237, Acc#117721] and "Absorption, Metabolism and Elimination of Thiabendazole in Farm Animals and a Method for its Estimation in Biological Materials" [J. Pharm. and Exp. Ther. 149, 263 (1965), See PP#3F1332, Acc#118042]. In the rat only 4 compound were isolated after administration of thiobendazole. These compounds

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were the unchanged parent, free 5-hydroxythiabendazole, the sulfate conjugate of 5-OH-TBZ, and the glucuronide conjugate of 5-OH-TBZ. Similar results were found for cattle, goats, pigs. In man, more that 40% of the administrated thiabendazole and its metabolite (and conjugates) were excreted in the urine within the first 4 hours, and approximately 80% within the first 24 hours. Therefore, the major metabolic pathway is hydroxylation at the 5-position with subsequent conjugation as the glucuronide and sulfate esters. The residues stated in the tolerance expression for animal products [40 CFR 180.242(b)] are the parent TBZ and its animal metabolite, 5-OH-TBZ.

No metabolic data has been submitted for poultry. As expressed in previous RCB reviews, this deficiency will be addressed in the registration standard. In addition, the Agency does not have immediate access to the ruminant metabolic data initially filed with FDA in regards to the use of thiabendazole as a animal drug (FDA's files, NDA 15-875 and NDA 15-123V). This deficiency can also be addressed in the registration standard. The need for additional analytical methodology will assessed after review of this metabolic data.

Analytical Method:

Residue data for stored corn grain and corn by-products were collected using submitted method entitled "Thiabendazole Determination In/on Corn Grain and Corn By-Products" (See PP#7F3553/7H5541, MRID#402717-06). This method involves an overnight enzymatic digestion of a milled corn grain sample with diastase, followed by extraction of this digested homogenate with ethyl acetate, backwash with dilute NaOH, extraction into dilute HCl, and measurement of fluorescence by spectrophotofluorometry.

Residue data for milk and animal tissues were collected using submitted methods entitled "Thiabendazole and 5-OH Thiabendazole Determination in Animal Tissue, Blood, And Milk" and "Thiabendazole and 5-OH Thiabendazole Determination in Animal Fat and Poultry Skin and Fat" (See PP#7F3553/7H5541, MRID#402717-07). This method involves an overnight enzymatic digestion in buffered solution with Glusulase™ (a commercially available enzyme mixture containing glucuronidase and sulfatase), then followed by an extraction of this digested mixture with ethyl acetate. After a series of purification washes, the thiabendazole is extracted from the organic solvent into dilute HCl and measured using spectophotofluorometry. The metabolite 5-OH-TBZ is reconstituted from the evaporated state with isopropyl alcohol/HCl solution and measured using a spectrophotofluorometric method.

After the extaction of the digest, the plant and animal methods follow similar procedures as those described in PAM II (Methods I, A, and B) and/or submitted in previous thiabendazole tolerance petitions. The major difference from the PAM methods is an initial enzymatic digestion of the sample to release any bound residues. The PAM II methods are adequate for enforcement of thiabendazole residues.

PAM II does not presently include methods for enforcement for residues of thiabendazole or its 5-OH metabolite, in cattle, horses, hogs, goats, sheep and poultry fat, meat, and meat byproducts, eggs, or milk, but RCB has submitted analtyical methodology for inclusion into PAM II (private communication, M. Bradley, RCB files) for milk (submitted as a letter method), and a literature reference [J. Pharm. & Exp. Ther., 149, 263 (1965)] for the analysis of animal tissues for thiabendazole, 5-OH thiabendazole, and its conjugates. A previous method validation of these methods were completed by FDA (See memo of 5/24/72, E. Gunderson, PP#1F1031) in regards to animal drug applications, NDA 15-875 and NDA 15-123V. Analytical methodology for thiabendazole (swine tissue, not for ruminants tissue or milk) was published in FDA's Food Additive Analytical Manual (FAAM, revised edition 1973), but was not included in the 1983 edition. In addition, FDA has recently investigated an HPLC method to modernize thiabendazole analytical methodology for milk and animal tissues (See thiabendazole s.f. (RCB files), FDA Contract#223-85-7086 status reports). Adequate validation and/or recovery for a variety of r.a.c.'s (sugar beets, citrus, white potato, soybeans, banana, and rice) are available from other petitions (See PP#'s 8F0674, 0F0881, OG1001, 5F1537, 5F1646, and 9F2216). No addition validation data is submitted in this petition but recovery data for corn grain and corn byproducts are given.

As corn is a major US commodity, and as the proposed use could be instituted in all growing areas, RCB would prefer a method for meat, milk, and eggs which utilizes a chemical hydrolysis, but we can accept an enzymatic hydroylsis if the petition provides a method for an analyst to confirm the specificity and activity of the enzyme as it is used for hydroylsis of any bound and/or conjugate residues of thiabendazole and/or the 5-OH metabolite. However, since FDA is working on updating the methodology, and will include methodology for milk (and a reference for animal tissue analysis) in PAM II, RCB will not withhold its recommendation for establishment of a thiabendazole tolerance in/on corn for this proposed use, but will recommend that this deficiency be addressed in the registration standard.

Residue Data:

The petitioner has submitted residue data (1984 and 1985 field trials from IL) from PP#5G3258 (EPA File No. 618-EUP-11), additional sampling data from same trials of the aforementioned EUP, and data from new trials located in IA, IL, IN, and MI. A total of 453 samples are reported; analyses of these samples were run in duplicate and include recovery and check samples. The residue data were collected using MERTECT 340-F in all trials except the 1984 IL field trial in which TECTO [oil base formulation containing 45% (w/v) thiabendazole] was used to treat the stored corn grain. A thiabendazole formulation was applied once and the treated corn grain sampled for residues.

The following table is a summary of the submitted data:

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Location, Trial #	Formulation	Spray vol fl oz/bu	a.i., oz/bu	Storage, weeks	# of samples	Residue range, ppm
IL 1984 (II)	TECTO (64661)	4	5 ppm *	0 - 40	66	2.60 - 5.46
"	"	"	10 ppm *	0 - 40	66	3.70 - 11.75
"	"	"	20 ppm *	0 - 40	72	7.43 - 22.00
"	none, ck	---	---	12	3	0.03 - 0.26
IL 1985 (I)	MERTECT 340-F	4	0.014	0 - 40	66	6.67 - 14.22
"	"	"	"	0 - 40	64	10.04 - 23.22
"	none, ck	---	---		2	0.00 - 0.75
IL 1985 (II)	MERTECT 340-F	4	0.014	0 - 24	24	11.98 - 23.58
IN 1985	"	3.8 - 5.9	"	0 - 26	24	8.54 - 10.04
"	none, ck	---	---	22 - 26	3	0.01 - 0.04
IL 1986 (I)	MERTECT 340-F	3	0.014	0	4	8.07 - 17.33
"	none, ck	---	---	1	1	0.00
IL 1986 (II)	MERTECT 340-F	3	0.014	0	8	11.40 - 17.49
IL 1986 (III)	"	"	"	"	4	8.15 - 13.20
IL 1986 (IV)	"	"	"	"	2	11.32 - 11.62
IL 1986 (V)	"	"	"	"	4	8.74 - 14.65
IL 1986 (VI)	"	"	"	"	4	17.56 - 22.46
IL 1986 (VII)	"	"	"	"	1	9.95 - 10.44
IL 1986 (VIII)	"	"	"	"	3	8.68 - 17.88
IN 1986 (I)	"	"	"	"	4	11.05 - 13.68
"	none, ck	---	---	"	2	8.15 - 13.20†
IN 1986 (II)	MERTECT 340-F	3	0.014	"	12	9.68 - 19.32
IA 1986 (I)	"	"	"	"	4	16.71 - 19.15
IA 1986 (II)	"	"	"	"	1	13.77 - 14.75
IA 1986 (III)	"	4	"	"	8	10.06 - 23.71
MI 1986 (I)	"	3	"	"	4	11.23 - 15.46

* oz/bu not given, only ppm/bu
† apparent sample contamination

The residue values ranged from 6.67 to 23.71, while the mean residue values ranged from 9.26 to 19.14, with only one trial above (22.30 ppm) the requested tolerances. In general the residue data shows that the requested tolerance of 20 ppm in/on corn grain will cover the estimated thiabendazole residues for the proposed use in this petition. The fluctuation of thiabendazole residues in treated corn grain seems to be dependent on the application technique and/or applicator, and/or storage conditions, e.g., air flow. The applied formulations were to give a final thiabendazole residue of approximately 20 ppm. Because treatment and sampling procedures may lead to fluctuations in measured residues in properly dosed corn grain, we recommend that the tolerance request be raised to 25 ppm for corn grain.

Although, the petitioner has submitted a low number of check samples, the analytical method is adequate and reliable so that additional blanks for corn grain will not be requested from the petitioner; the check samples were sampled from 0 to 26 weeks. No new recovery data are reported in this petition [No recovery data for corn grain are included in the material received by RCB as stated by petitioner (See p8, MRID#402717-05)]. The recovery data submitted in the EUP (See PP#5G3258) are also referenced: (spiked level, % recovery) 0.10 ppm, 93; 0.40 ppm, 97; 2.00 ppm, 96; 10.00 ppm, 106. The recovery data from the EUP is adequate for corn grain and additional recovery data for corn grain will not be requested by RCB for the proposed use.

Grain Dust: The petitioner needs to submit residue data for grain dust which reflects the proposed use. RCB suggests that the petitioner add untreated dust to cleaned grain (free of dust), tumbled to mix the grain and dust, followed by treatment, collection (an air stream), and analysis. The typical yield of corn dust in a commercial operation is about 0.2%, i.e., 90 g of dust/100 lb of corn grain. If the petitioner needs assistance in the design of an adequate system to generate the data, Dr. C. Parnell, Professor, Department of Agricultural Engineering, Texas A & M, has developed a model system for the generation and collection of corn grain dust with a laboratory tumbler. The petitioner can also submit a protocol for Agency review and comments.

Storage stability data have been submitted for sugar beets (7 months at -40°F, See PP#0F0881), apples (10 months at -30°F, See PP#1F1031), and white potatoes (30 months at +45°F, See PP#5F1537). Data are submitted in this petition for up to 40 weeks at ambient temperature. Thiabendazole residues are stable under these conditions as evidenced by the submitted residue data; therefore the storage stability data is adequate for the purposed use.

Corn processing studies:

Two studies have been submitted for dry processing of treated corn grain, one using MERTECT 340-F and the other using ARBOTECT 20S. According to the residue data, residues concentrate in bran, fines,

germ (raw and defatted), and soapstock. There are no concentrations of thiabendazole residues in oil (crude or refined), gruel (whole grain or degermed), or flour (whole grain or degermed). Also the residue levels are similar in all processed products independent of the formulation used in the treatment.

The following table is a summary of the submitted data:

Processed Commodity	Residue range, ppm		
	MERTECT 340-F	ARBOTECT 20S	Check
grain	15.70 - 21.57	16.38 - 21.64	0.00 - 0.05
fines	27.63 - 35.26	33.52 - 37.72	0.18 - 0.20
bran	109.0 - 124.2	95.6 - 106.0	0.02 - 0.04
grits	6.13 - 6.86	6.41 - 6.70	0.00 - 0.02
raw germ	19.30 - 26.51	16.44 - 20.74	0.02 - 0.34
defatted germ	25.57 - 29.60	19.58 - 22.81	0.00 - 0.03
crude oil	5.86 - 9.51	4.14 - 4.86	0.00 -0.01
refined oil	6.55 - 7.50	2.94 - 3.23	0.01
soapstock	21.30 - 22.68	8.75 - 9.98	0.18 - 0.21
degermed/gruel	0.87 - 0.97	0.90 - 0.94	0.00
whole grain/gruel	2.61 - 2.72	2.74 - 2.85	0.03
degermed/flour	6.77 - 7.02	6.54 - 6.62	0.00 - 0.02
whole grain/flour	17.72 - 19.30	17.72 - 18.85	0.18

Recovery data are given for the following processed commidities: (ppm, % recovery); grain (0.10-10.0, 93-106%); bran (40-120, 89-109%); raw germ (5.0-20.0, 95-104%); defatted germ (13.33, 98%); crude oil (10.0, 92%); soapstock (5.0-20.0, 97-102%).

Based on this data there is a concentration of residues in the bran, fines, germ, and soapstock:

$$\frac{\text{residue bran}}{\text{residue grain}} = \frac{124 \text{ ppm}}{21.6 \text{ ppm}} = 5.7$$

$$\frac{\text{residue fines}}{\text{residue grain}} = \frac{35.2 \text{ ppm}}{21.6 \text{ ppm}} = 1.6$$

$$\frac{\text{residue raw germ}}{\text{residue grain}} = \frac{26.5 \text{ ppm}}{21.6 \text{ ppm}} = 1.2$$

$$\frac{\text{residue defatted germ}}{\text{residue grain}} = \frac{29.6 \text{ ppm}}{21.6 \text{ ppm}} = 1.4$$

$$\frac{\text{residue soapstock}}{\text{residue grain}} = \frac{22.7 \text{ ppm}}{21.6 \text{ ppm}} = 1.05$$

The petitioner has suggested that feed additive tolerances be established for corn bran (125 ppm), corn fines (40 ppm), corn germ (30 ppm), and soapstock (25 ppm). Based on the above data, if and when a thiabendazole tolerance is established for corn grain, then feed additive tolerances should be established at the following tentative levels (see additional data requirements below):

corn, milled fractions (exc bran and soapstock)(post-H)	40 ppm
corn bran (post-H)	145 ppm

No feed additive tolerance is needed on soapstock at this time.

Based on this data, if and when a thiabendazole tolerance is established for corn grain, then food additive tolerances should be established at the following tentative levels (see additional data requirements below):

corn, milled fractions (exc bran) (post-H)	40 ppm
corn bran (post-H)	145 ppm

Also based on this data, there is no concentration of residues in the grits, crude oil, refined oil, degermed gruel, whole grain gruel, degermed flour, or whole grain flour.

$$\frac{\text{residue grits}}{\text{residue grain}} = \frac{6.86 \text{ ppm}}{21.6 \text{ ppm}} = 0.32$$

$$\frac{\text{residue crude oil}}{\text{residue grain}} = \frac{9.51 \text{ ppm}}{21.6 \text{ ppm}} = 0.44$$

$$\frac{\text{residue refined oil}}{\text{residue grain}} = \frac{7.50 \text{ ppm}}{21.6 \text{ ppm}} = 0.35$$

$$\frac{\text{residue degermed gruel}}{\text{residue grain}} = \frac{0.97 \text{ ppm}}{21.6 \text{ ppm}} = 0.05$$

$$\frac{\text{residue whole grain gruel}}{\text{residue grain}} = \frac{2.72 \text{ ppm}}{21.6 \text{ ppm}} = 0.12$$

$$\frac{\text{residue degermed flour}}{\text{residue grain}} = \frac{7.02 \text{ ppm}}{21.6 \text{ ppm}} = 0.32$$

$$\frac{\text{residue whole grain flour}}{\text{residue grain}} = \frac{19.3 \text{ ppm}}{21.6 \text{ ppm}} = 0.89$$

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Note: Any need for a feed additive tolerance for grain dust will be assessed after residue data for grain dust is submitted and reviewed.

The bulk of the US annual corn crop is used for animal feed or exported. The remaining 10% is processed by either a wet or a dry milling process. Approximately 80% is milled by the wet method vs 20% by the dry method. The petitioner has submitted data for a dry milling process only. Normally RCB would like to review data from both processes for corn grain.

The wet milling process yields starch, syrups, oil, and feed byproducts (e.g., steep liquor, spent germ). Based upon the proposed postharvest use of thiabendazole on stored corn grain little, if any residue, will be translocated from the exterior of processing. Any thiabendazole residues would be on the surface and most of these residues would be concentrated in the steep liquor faction of the wet milling process. The steep process involves treatment of corn in warm water at 120-125°F for about 2 days (SO_2 treated to prevent fermentation), and removal and concentration of steepwater to give thick syrup that is added to feeds. Since thiabendazole solubility in water pH 5-12 is <50 mg/L, residues should not concentrate in the starch, syrup, or oil fractions. But the need for any feed additive tolerances for concentrated steep liquor, starch, oil, or other milling fractions can not be adequately determined without residue data for these processed commodities; therefore the petitioner should submit residue data for the wet milling process.

Meat, Milk, Poultry, and Eggs:

Lactating cows were dosed daily with 10 ppm of thiabendazole for 4 weeks, then fed an additional 4 weeks at a 30 ppm level. Milk samples were analyzed at the end of weeks 3 and 7 for thiabendazole, 5-hydroxythiabendazole, and conjugates (See PP#0G1001, Acc#116748). The samples did not differ much from controls (<0.03 ppm TBZ, <0.05 ppm 5-OH-TBZ); only one sample (30 ppm feeding level) showed detectable residue of 5-OH-TBZ (0.17 ppm); three other samples (30 ppm feeding level) gave residues at the limit of detection (0.05 ppm). No detectable residues (<0.03 ppm) of TBZ were found in any milk samples.

In this petition (PP#7F3553/7H5541, See MRID#402717-07)), a thiabendazole feeding study at levels of 25 ppm (1X), 75 ppm (3X), and 250 ppm (10X), were conducted with lactating cows . [These levels had previously been recommended by the Agency (See memo of 9/9/86, J. Garbus)]. Cows were dosed daily for 28 consecutive days, then sacrificed on day 29 or day 57 and the tissues, fat, liver, kidney, and blood were analyzed for combined residues of thiabendazole and its 5-hydroxy metabolite.

The following table is a summary of residue data:

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Animal Product	Residue levels, ppm		
	25 ppm dose *	75 ppm dose *	250 ppm dose *
milk: (2-28 days)			
TBZ	<0.05†	<0.05	<0.05
5-OH-TBZ	"	0.016 - 0.148	0.064 - 0.246
milk: (35-57 days)			
5-OH-TBZ	"	"	"
fat: (day 29)			
TBZ	"	"	"
5-OH-TBZ	"	"	"
fat: (day 57)			
TBZ	"	"	"
5-OH-TBZ	"	"	"
kidney: (day 29)			
TBZ	"	"	"
5-OH-TBZ	"	0.094 - 0.468	0.316 - 0.553
kidney: (day 57)			
TBZ	"	<0.05	<0.05
5-OH-TBZ	"	"	"
liver: (day 29)			
TBZ	"	0.041 - 0.131	0.054 - 0.083
5-OH-TBZ	"	0.035 - 0.061	0.120 - 0.161
liver: (day 57)			
TBZ	"	<0.05	<0.05
5-OH-TBZ	"	"	"
tissue: (day 29)			
TBZ	"	"	"
5-OH-TBZ	"	"	"
tissue: (day 57)			
TBZ	"	"	"
5-OH-TBZ	"	"	"

* 25 ppm = 1X feeding level; 75 ppm = 3X feeding level; 250 ppm = 10X feeding level

† sensitivity of method

If the tolerances for grape and processed grape products are revoked, then a typical dairy cattle diet may consist of 50% corn grain (20 ppm, proposed), 25% apple pomace (33 ppm), and 25% potato waste (30 ppm) for a "worst case" dietary burden of 25.8 ppm. From the above residue data, the established tolerance of 0.4 ppm for milk would not be exceeded. Even if a typical diet consisted of a high percentage of corn processing byproducts, e.g., 50%, the submitted residue data shows that the 0.4 ppm milk tolerance is still adequate for the proposed postharvest use. There would also be little likelihood that high percentages grape pomace (150 ppm) and corn bran (120 ppm, proposed) would be included together in a typical cattle diet.

If the grape tolerances are not revoked, and the tolerances are established for corn grain and processed byproducts, then a "worst case" dietary burden would be 59 ppm. From the above residue data, the established tolerance of 0.4 ppm for milk would not be exceeded. At this exposure level the established 0.1 ppm tolerances in 40 CFR 180.242(b) for meat byproducts for cattle, goats, hogs, horses, and sheep should be changed to following: meat byproducts (exc. liver, kidney) 0.1 ppm, liver, 0.4 ppm, and kidney, 0.4 ppm; fat and meat tolerances remain 0.1 ppm.

A poultry feeding study was submitted in an amendment to PP#6F1860 in which three-day-old broiler chicks were fed a diet containing 0, 2, 20, 200, or 2000 ppm TBZ for 46 days. The following table is a partial summary of data:

Animal product	Residue level, ppm †		
	2.0 ppm dose	20 ppm dose	200 ppm dose
tissue:	<0.05	<0.05	0.035 - 0.093
skin/fat:	"	"	0.053 - 0.102
kidney:	0.040 - 0.081	0.068 - 0.121	0.328 - 0.847
liver:	<0.05	0.056 - 0.081	0.204 - 0.631
egg yolk:	NR	0.023 - 0.053	0.071 - 1.31
egg white:	NR	<0.05	0.047 - 0.648

† combined residues of thiabendazole and 5-OH-thiabendazole
NR: not reported

A typical poultry diet can consist of 70% corn grain (25 ppm), 20% potatoes and waste (10.0 ppm), and 10% wheat grain (1.0 ppm) for a "worst case" dietary burden of 19.6 ppm. The established tolerances of 0.1 ppm for poultry, and for eggs are not likely

to be exceeded, except for poultry kidney. Therefore a tolerance should be established for poultry kidney at 0.2 ppm, and poultry meat byproducts should be changed as follows: poultry meat byproducts (exc kidney), 0.1 ppm. A revised Section F should be submitted.

RCB concludes that this proposed postharvest use for stored corn grain is covered by 180.6(a) with respect to milk (section 2) and with respect to meat, poultry, and eggs (section 3).

Other Considerations:

As stated earlier (See Nature of the Residue, animal metabolism, this memo), the metabolism of thiabendazole has been reported for livestock animals, laboratory rat, and man. Thiabendazole is also presently used as an anthelmintic. FDA approved dose levels for a 3-day treatment can be as high as 50g/1000 lb cow. According to 21 CFR 520.2380, the milk can not be used during this treatment period and within 96 hours post-treatment; cattle cannot be slaughtered within 3 days; a 0.05 ppm tolerance is established (21 CFR 556.730) for negligible residues. Pigs, sheep, and goats have a 30-day post-treatment slaughter interval (PSI). This type of restriction is not necessary for the proposed postharvest use for stored corn grain and in fact would not be practical for treated corn grain; the established milk tolerance of 0.4 ppm will cover any secondary residues of thiabendazole and its metabolite, 5-OH-TBZ (40 CFR 180.242) for this proposed use. Tolerances of 0.1 ppm are established for the combined residues of thiabendazole and its metabolite, 5-OH-TBZ, in livestock meat, fat, and meat byproducts, and eggs [40 CFR 180.242(b)], while a 0.1 ppm tolerance is established for negligible residues of thiabendazole only for an animal drug use in uncooked edible tissues of cattle, goats, sheep, pheasants, and swine (21 CFR 556.730).

Note: If and when a thiabendazole tolerance is established for corn grain, then FDA should be notified (cc: C. Kennedy, Center for Veterinary Medicine, FDA) of Agency action.

Grape and grape pomace tolerances:

The petitioner has requested revocation of the 10 ppm tolerance for grapes and the 150 ppm tolerance for grape pomace. However, on review of the submitted ruminant feeding study, the established tolerances in 40 CFR 180.242(b) would not be exceeded with the establishment of the proposed tolerance for corn grain and still allowing the grape tolerances to remain as such. Therefore, it not necessary to revoke the grape tolerances for any RCB concerns at this time. If there are no other data requirements, then a revised Section F should be submitted (if it is the desire of the petitioner to retain the established grape tolerances).

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Codex considerations:

There are no Canadian or Mexican limits for thiabendazole in/on corn grain. A Codex tolerance of 0.2 ppm is established for cereal grains, but for plant products only and for parent only. Likewise Canadian and Mexican thiabendazole tolerances for other plant products are for parent only. A 25 ppm tolerance is necessary since the submitted residue data establish the need for this level. Therefore non-compatability exists between Codex, Canadian, and Mexican limits and the proposed U.S. tolerances for corn grain and processed feed products.

Attachment 1: Confidential Appendix (1 page)
Attachment 2: International Residue Limit Status (1 page)
cc with Attachments 1 and 2: R.F.; PMSD/ISB; PM-21; J. Stokes; Thiabendazole S.F.
cc with Attachment 2 only: Circu
RDI: PErrico:7/20/88:RSchmitt:7/21/88
TS-769:RCB:JStokes:js:Rm 805:CM#2:7/21/88

Page 18 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ _____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

_____ Internal deliberative information.

_____ Attorney-Client work product.

_____ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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