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

OCT 31 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#5G3258/618-EUP-RR. RCB Non-concurrance
Re: Use of Thiabendazole on Stored Corn.

FROM: Charles L. Trichilo, Ph.D., Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Henry M. Jacoby, PM-21
Fungicide-Herbicide Branch
Registration Division (TS-767)

In the RCB memo dated September 10, 1985 by L. Cheng, we recommended against the above-cited petition. RCB requested a corn processing study and a large animal feeding study be conducted for a favorable recommendation.

Based on input from the Toxicology Branch indicating a lack of concern for this use, we have reevaluated our position and find we could recommend favorably provided:

1) Corn that has been treated will be used for animal feed only.

2) A 3(c)(2)(B) letter is sent to the Company requesting a large animal feeding study (see our above-cited memo for details).

This change in position results from the fact that currently established tolerances are the major reason for the need for a new feeding study and not this EUP. Also, removing the direct exposure pathway of corn to humans mitigates against the need for a processing study for this EUP.

cc: Melone, HED

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

SEP 10 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#5G3258. Thiabendazole (TBZ) on Stored Corn. Evaluation of Analytical Method and Residue Data. Accession Number 073589. RCB Number 1229.

FROM: Leung Cheng, Chemist L. Cheng
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Henry Jacoby, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Merck, Sharp and Dohme has requested an Experimental Use Permit (EPA File No. 618-EUP-RR) for use of its thiabendazole-containing product MERTECT 340-F (EPA Registration No. 618-75) on stored corn grain. A temporary tolerance of 20 ppm of thiabendazole on corn grain has been proposed. The regulation when established should note this is a post-harvest use.

Tolerances have been established for residues of thiabendazole [2-(4-thiazolyl)benzimidazole] from post-harvest use in/on apples, bananas, tops of sugar beets and citrus fruit at 3 to 10 ppm. Tolerances have also been established for the combined residues of thiabendazole (TBZ) and its metabolite 5-hydroxythiabendazole in meat, fat, meat by-products of cattle, goats, hogs, horses, poultry and sheep, and eggs at 0.1 ppm. Tolerance on milk is set at 0.4 ppm [40 CFR 180.242].

Feed additive tolerances are also established. These include 150 ppm on grape pomace and 30 ppm on potato processing waste [21 CFR 561.380].

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Merck has requested to ship 232 lbs of the active ingredient to be tested on 260,000 bushels (equivalent to ca 15 million lbs of corn grain) of corn harvested in the States of Illinois, Indiana, Iowa and Michigan. The experimental program is to last from September 1985 to August 1987.

A registration standard on thiabendazole has not been issued.

Conclusions

1. We repeat our previous conclusion in that the residue of concern is TBZ on plants, and TBZ and its metabolite 5-hydroxy-TBZ in animals.

2. An analytical method is available for enforcement of the proposed tolerance on corn grain. Methods for analyzing TBZ residues in meat, milk, poultry and eggs are also adequate.

3a. The proposed temporary tolerance of 20 ppm is adequate to cover the residues on corn grain.

3b. Since corn grain can be processed into crude and refined oil, and milled products, a processing study is required. Food/feed additive tolerances may be required.

4a. Feeding study data generated other than from continuous feeding for 4 weeks are no longer acceptable (see p. 22-23 of Pesticide Assessment Guidelines, Subdivision O, October 1982). As a result, there is a lack of appropriate feeding study data in animal tissues and the established 0.1 ppm meat tolerance may not be adequate to cover the residues in meat, fat and meat by-products from all uses involving TBZ. We are also unable to project a meaningful meat tolerance level in the absence of appropriate feeding study data. A cattle feeding study which includes the expected level of intake plus two exaggerated levels of 3X and 10X will be needed.

4b. The estabalished 0.4 ppm milk tolerance will be adequate to cover TBZ residues from proposed use.

4c. Tolerances on poultry meat, fat and meat by-products, and eggs will adequately cover any transfer of secondary residues including from this proposed use.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Recommendation

We recommend against this temporary tolerance petition and the experimental use permit for reasons cited in Conclusion 3b and 4a. These deficiencies must be resolved for further consideration on this application.

Additional residue data should accompany a permanent tolerance petition.

DETAILED CONSIDERATIONS

Manufacture and Formulation

The synthesis of thiabendazole (TBZ) is described in the review of R. Schmitt (PP#5F1646 October 17, 1975). Technical TBZ is 98.5 percent pure and contai

The impurities are not likely to pose a residue problem. MERTECT 340-F contains 42 percent TBZ (3.8 lbs ai/gallon). The remaining inert ingredients have been cleared under 180.1001 for use on food crops (PP#2F2603, M. Bradley, February 8, 1982).

Proposed Use

The fungicide is intended to be used at a rate of 0.03 fl oz (0.015 oz ai) per bushel for control of Aspergillus spp. and Penicillium spp. during low temperature drying and long term grain storage. A standard bushel of corn grain weighs 56 lbs. Since corn grain contains 15 to 20 percent moisture content after drying, the treatment concentration is ca 20 ppm on a dry weight basis.

Nature of the Residue

The fate of TBZ from post-harvest use on treated citrus (PP#8F0724) and apples, crabapples and pears (PP#1F1031) was discussed in connection with PP#1F1031 (E. Gunderson, December 29, 1970). A radiotracer study submitted in PP#8F0724 shows that residues of TBZ remain predominantly in the peel of the fruit. Studies with cotton and soybean seedlings using ^{14}C-TBZ and pepper and tomato seedlings using unlabeled TBZ indicate that TBZ is absorbed and translocated by plants through the roots without alteration or binding with plant constituents (PP#2F2603, M. Bradley, February 8, 1982). We conclude the residue of concern resulting from post-harvest application of TBZ is the parent compound.

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The metabolic fate of TBZ in animals has been discussed in detail by W. Boodee (PP#8F0674, March 8, 1968). The major metabolic pathway is hydroxylation at the 5-position with subsequent conjugation as the glucuronide and sulfate esters. In our more recent review, it was stated that data in a published article [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)] "demonstrate that neither TBZ nor its primary metabolite 5-hydroxy-TBZ has a tendency for tissue storage" in cows and goats once dosed with 50 to 225 mg/kg (M. Bradley, February 8, 1982, PP#2F2603). These tissue studies, analyzed by both radiometric and chemical assays, were submitted for new drug applications (NDA 15-875 and ND A15-123V). We repeat our previous conclusion that the residue of concern consists of TBZ and its metabolite 5-hydroxy-TBZ.

NOTE: As far as we can determine, no conventional poultry metabolism study has been submitted to date.

Analytical Method

Two methods were used to collect residue data: (1) "Thiabendazole Determination in/on Corn Grain" which incorporates an exhaustive hydrolysis step and (2) "Thiabendazole Determination on Corn Grain via Surface Rinse" which does not involve a hydrolysis step. Method (1) closely resembles method A (Thiabendazole Residues in Banana Peel and Pulp) in PAM II. Briefly, the corn grains are thoroughly milled and digested in water containing 1N H_2SO_4 and 0.1N HCl on a steam bath. The mixture after cooling is adjusted to pH 4 to 4.5 with 2N NaOAc. The sample is further digested with diastase (which converts starch to malt sugar) at 45 to 50 °C. To an aliquot of this mixture is added NaCl and 2N NaOAc, and extracted with ethyl acetate three times. The combined organic layer is washed with NaOH and water. The residues are extracted into 0.1N HCl which is then rendered alkaline with 2N NaOH. TBZ residues are again extracted into ethyl acetate. The acid extraction is repeated, and the acid phase is examined for TBZ residues spectrophotofluorometrically.

Method(2) involves sonicating whole kernels in 0.1N HCl several times. An aliquot of this acid extract is rendered alkaline and TBZ residues are extracted into ethyl acetate. TBZ residues are back-extracted into 0.1N HCl which is examined on a spectrophotofluorometer.

Control samples had 0.09 ppm or less TBZ. For method (1) 104 & 107 percent recovery values were obtained when milled grain samples were fortified with 10 ppm TBZ. There are no validation

data for Method (2). However, recoveries of 85 to 87 percent were obtained at 20 to 25 ppm fortification levels for a less rigorous rinse method (essentially method (2) without sonication).

Method (1) is adequate for enforcement of the proposed tolerance on corn grain.

Residue methods on meat and milk were found to be adequate at sensitivities of 0.05 ppm (milk) and 0.1 ppm (meat) (PP#8F0724/ FAP8H2298, B. Hopkins, August 23, 1968).

Methods are available for enforcing residues of TBZ and 5-hydroxy-TBZ in poultry tissues and eggs. These are modification of the PAM II and Food Additives Analytical Methods (PP#6F1860, E. Leovey, August 6, 1979).

Residue Data

Trials were carried out at the University of Illinois. Two formulations were used: an oil based TECTO which is an acceptable alternate for MERTECT 340F (letter by H. Jacoby dated April 11, 1985) and an acid based ME-147 which is essentially ARBOTECT 20-S (EPA Registration No. 618-88) plus small amounts of wetting agents. Treatment rates ranged from 5 to 100 ppm TBZ with respect to weight of corn grain treated. Following treatment, the grains were stored at ambient temperature, then sampled at various intervals from 0 to 140 days. After sampling, the grains were immediately frozen and shipped with or without dry ice for analysis. Samples were maintained at 2 to 5 °C or less in the laboratory before analysis. Only the 20 ppm samples were analyzed by both method (1) and (2). Time between these treatments and analyses was not given.

Residue data from 1984 Illinois Trial I and II resulting from the 20 ppm TBZ treatment are tabulated below.

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Day After Treatment	Formulation	TBZ Residue on Corn (ppm) Method (1)	Method (2)
0	TECTO	11.09, 11.23	8.78, 9.32
42		10.31, 11.59	6.56, 7.79
73		11.20, 11.37	6.74, 8.56
0	ME-147	14,84, 15.76	12.48, 15.72
42		13.68, 15.68	8.41, 13.36
73		15.50, 16.09	9.26, 10.60
0	TECTO	11.13-17.21, 22.0	7.15-13.12, 20.10
28		9.40-18.38	4.93-12.08
56		7.43-15.20	5.70-12.03

Except for two values, residues on treated corn are less than the theoretical treatment concentration of 20 ppm. Loss of TBZ residues on storage appears to be insignificant. As expected, residues determined by the exhaustive hydrolysis method (method (1)) are higher than the less rigorous Method (2). We believe the 22.0 ppm and 20.10 ppm residue values are due to uneven application or sample contamination. The proposed temporary tolerance of 20 ppm is adequate to cover the residues on corn from the proposed TBZ treatment. Additional residue data will be required for a permanent tolerance petition.

Field corn can be processed to yield crude oil, refined oil and milled products. No data have been submitted on these processed commodities. A processing study is required and food/feed additive tolerances may need to be proposed.

Meat, Milk, Poultry and Eggs

A conventional cattle feeding study was submitted in PP#0G1001. Three lactating dairy cattle were fed TBZ in the diet equivalent to 10 ppm continuously for 4 weeks. This was immediately followed by feeding the same cattle at a 30 ppm TBZ dietary level for 4 additional weeks. Only milk samples were analyzed. No analyses on tissue samples were reported. At the 10 ppm feeding level no detectable residues of TBZ (<0.03 ppm) or 5-hydroxy-TBZ (<0.05 ppm) were noted in milk samples. From the 30 ppm feeding level, four samples contained 0.05 ppm and one had 0.17 ppm 5-hydroxy-TBZ. The remaining seven samples had no detectable 5-hydroxy-TBZ residues. All samples showed no detectable (<0.03 ppm) residues of TBZ.

Grape pomace (150 ppm tolerance) may constitute up to 20 percent maximum of dairy cattle diet. Dietary burden of TBZ from this feed item would be 30 ppm. Assuming the dairy cattle injest another 50 percent field corn grain (20 ppm proposed tolerance) in their diet, the total dietary burden would be 40 ppm. From the above milk residue data, the established 0.4 ppm milk tolerance is not likely to be exceeded.

Some drug residue data published in J. Pharm. & Exp. Ther. 149 263 (1965) were previously discussed in PP#1F1031 by E. Gunderson (memo of May 24, 1972). Calves and goats were orally dosed once at levels of 50, 110, 150 or 200 mg TBZ per kg body weight. Three days after the lowest dose (50 mg/kg approximates 1700 ppm in calves diet and 1250 ppm in goats diet) residues found in a calf were < 0.2 ppm in fat, heart, kidney, liver and muscle. Calf skin contained the highest residue of 0.46 ppm. When another calf was sacrificed 30 days after the same dose of 50 mg per kg, < 0.08 ppm TBZ residues were detected in all tissues. Five goats were dosed at the 50 mg/kg level. One goat sacrificed on day 1 showed residues of < 0.08 ppm in fat, 0.3 ppm in heart, 2.7 ppm in kidney, 1.1 ppm in liver and 0.3 ppm in skin. The day-17 goat showed < 0.08 ppm in fat, kidney or skin, 0.2 ppm in heart and liver. The remaining goats contained < 0.08 ppm TBZ residues in all tissues on day 30. While the above data show low residues in tissues as a result of high feeding dose levels, these tissue residue studies were designed to support veterinary drug use and in this case, TBZ label specifies a 30-day withdrawal period. Such withdrawal periods are not practical in pesticide uses since animals may be fed treated feed items up to time of slaughter (p. 3, memo dated May 24, 1972, PP#1F1031). The above data are no longer adequate in estimating TBZ residues in animal tissues from animals ingested feed items containing high levels of TBZ residue (such as 150 ppm in grape pomace). The established 0.1 ppm meat tolerance may not be sufficient to cover the residues in animal tissues from all pesticide uses involving TBZ. We are also unable to project a meaningful meat tolerance level in the absence of appropriate feeding study data. A cattle continuous feeding study which includes the expected level of intake (this 1X level should represent the worst case estimate of the potential livestock exposure) and two exaggerated levels of 3X an 10X will be needed.

A poultry feeding study was submitted in an amendment to PP#6F1860. Three-day old broiler chicks were fed a diet containing 0, 2, 20, 200 or 2000 ppm TBZ for 46 days. Four hours after the diet was removed, three males and three females at each dose level were sacrificed. At the 20 ppm feeding level, combined residues (in ppm) of TBZ were

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0.017 to 0.023 in muscle, 0.024 to 0.028 in skin/fat, 0.068 to 0.121 in kidney and 0.056 to 0.081 in liver. Those resulting from the 200 ppm feeding level were 0.035 to 0.067 ppm, 0.056 to 0.102 ppm, 0.328 to 0.847 ppm and 0.204 to 0.631 ppm, respectively. Laying hens were also fed TBZ-containing diet at the same five levels for 21 days. The next three eggs laid by each hen after termination of dose were collected for residue analysis. Combined residues of TBZ were 0.007 to 0.022 ppm (whites) and 0.023 to 0.05 ppm (yolk) at the 20 ppm level, and 0.07 to 0.66 ppm (whites) and 0.044 to 1.31 ppm (yolk) at the 200 ppm level.

A poultry diet may consist of 70 percent corn grain, and 30 percent dehydrated and cull grapes (10 ppm tolerance). The total dietary burden would be 17 ppm TBZ residues. The established tolerance of 0.1 ppm on poultry and eggs is not likely to be exceeded.

cc: Circ, RF, SF, Cheng, TOX, EEB, EAB, PP#5G3258, FDA, Robert Thompson (RTP), PMSD/ISB.

RD/Section Head:A.R.Rathman:Date:8/28/85:R.D.Schmitt:Date:8/28/85
TS-769:Reviewer:LeungCheng:CM#2:Rm.810:557-7484
KENDRICK CONTRACT TYPING:DATE:9/6/85:PHONE NUMBER:898-1270
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 9 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA No. 618-EUP-11: Thiabendazole; Revised Protocol for Animal Feeding Study. No Accession Number RCB No. 1222

FROM: Joel Garbus, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THROUGH: A. R. Rathman, Section Head
Special Registration section I
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: H. Jacoby, PM-21
Registration Division (TS-767)

Merck, Sharp and Dohme has submitted a revised protocol for a large-animal feeding study to be conducted with its thiabendazole-containing fungicide Mertec 340-F. The company had petitioned for an Experimental Use Permit for the treatment of stored corn grain with thiabendazole. RCB's review of the petition (5G3258) noted that there was a lack of an appropriate feeding study to support the established tolerance of 0.1 ppm in meat, fat, and meat by-products. RCB pointed out that the studies cited in support of the tolerance involved a single large oral dose and did not reflect the possible continuous ingestion of treated grain. Therefore, the RCB review requested a cattle study involving the feeding of the material for at least 28 days at the maximum level expected in feed plus two exaggerated levels of 3X and 10X. (L. Cheng, memo of 9/10/85)

In response, Merck, Sharp and Dohme submitted a protocol entitled: "Cattle Residue Studies: Tissues.", a generic animal feeding protocol. The protocol as presented did not contain the name of the test material, the dosages or the analytical methodology to be used. The specific details are to be supplied for the specified compound. However, the experimental design, i.e., the number of animals to be used, the schedule of dosing, the design of controls, and the nature and scheduling of the examination of tissues, was given in detail and appeared to be adequate and acceptable.

Merck, Sharp and Dohme indicated that the dosages of thiabendazole that were to be employed were to be 16, 32, and 160 ppm. The 16 ppm was calculated as the 1X level that could be ingested by beef cattle (corn = 80% of feed X tolerance level of 20 ppm = 16 ppm.) However, RCB pointed out that a tolerance of 150 ppm was

established for dried grape pomace and that this commodity is a possible component of cattle feed. If cattle were to be fed grape pomace (residue 150 ppm) in addition to corn grain the level could be higher than the 16 ppm proposed by the company. We calculated that the worst case estimate would result from the unlikely feeding of 70% thiabendazole-treated corn grain plus 30% treated dry grape pomace. This could result in feed with 59 ppm of thiabendazole. Therefore we suggested that the levels to be used in the feeding study be 60, 180 and 600 ppm. (J. Garbus, memo 3/17/86)

The Petitioner has taken exemption to RCB's devising a highly unlikely and extreme worst case diet. They also point out that there is very little use of thiabendazole on grapes and that the product is not registered for use in California, the major source of grape pomace. Merck, Sharp and Dohme has, therefore, submitted a revised protocol for an animal feeding study that is identical to the one prviously proposed except that company will use 25 ppm as the 1X base rate. The company has arrived at this figure by: 1) voluntarily offering to cancel the registration for the use of grapes, concurrently with the filing of the petition for the permanent registation of the corn grain use, 2) basing the feeding level for the proposed studies on a diet consisting of 70% corn grain and 30% dried citrus pomace. (Citrus pomace at 35 ppm has the second highest of the currently registered tolerances.) In the interim, the company proposes to remove the use on grapes from labels, to inform all customers and agricultural chemical advisors of this fact, and to sell presently labeled thiabendazole immediately and deplete the current inventory completely by October 1986.

Comment:

RCB has no objection to Merck, Sharp and Dohme's proposed cancellation of the registration of thiabendazole on grapes. We reiterate our acceptance of the proposed protocol as suitable and adequate for the lactating ruminant feeding study. As the feeding level for the study as currently proposed will be equivalent to the maximum level possible if the use on grapes were cancelled, we consider the proposed level of 1X = 25 ppm as acceptable .

cc: R. F., S. F., PP#5G3258, Circ. Reviewer, PMSD/ISB
RDI:ARR:9/9/86:RDS:9/8/86
TS-769:RCB:JG:jg:CM#2:557-1864:9/8/86

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