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

AUG 11 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP No. 1F3974. Propiconazole on Grass Grown for Seed. Amended GLP Statement for MRID No. 41823305. CB No. 9924. DP No. D178453. MRID No. 42303800, -01.

FROM: Stephanie H. Willett, Chemist
Tolerance Petition Section 2
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

THRU: Elizabeth T. Haeberer, Section Head
Tolerance Petition Section 2
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

Elizabeth T. Haeberer

TO: Susan Lewis/Jim Stone, PM Team 21
Registration Division (H7505C)

Ciba-Geigy submitted PP No. 1F3974 in request for permanent tolerances for propiconazole in grass straw, forage and seed screenings. Ciba-Geigy has informed the agency that one of the contractors involved in one of the residue studies, the results of which were reported in MRID No. 41823305, was not in compliance with GLP requirements. An amended GLP statement for this report was submitted. However, the registrant has also informed us that the entire study has since been repeated and new data will be submitted to replace MRID No. 41823305.

This residue study was reviewed by CBTS in the 6/11/91 memo of S.H. Willett. The study data were found to be inadequate, and were not considered in determining the appropriate tolerances for grass straw, forage and seed screenings. CBTS requested additional data. Therefore, the discovery of noncompliance with GLP requirements does not impact upon our previous conclusions. Additional residue data are needed in support of the proposed tolerances, as was previously indicated.

cc: PP Nos. 1F3974, SWillett, E. Haeberer, RF, Circ
CM2:H7509C:RM803:3056439:SHWillett:shw-8/7/92
RDI: E. Haeberer, 8/10/92; R. Loranger, 8/10/92

Propiconizole Meeting

Phase 4 completed - 6/25/92
DCI received - 10/6/93

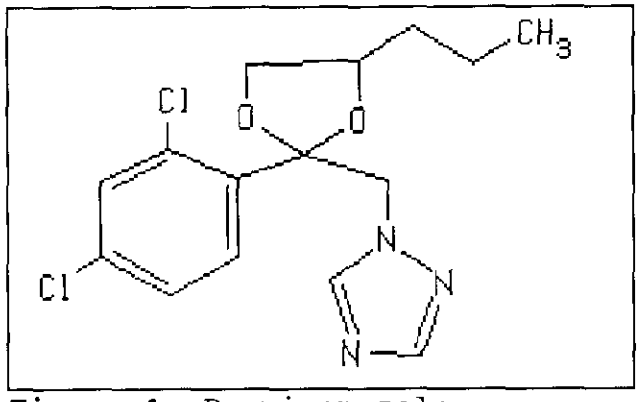

Figure 1 Propiconazole

Ruminant metabolism

M. Flood, 9/20/93 memo recommends for the establishment of tolerances in grasses grown for seed as follows:

Grass seed screening	60 ppm
Grass Hay (straw)	40 ppm
Grass Forage	0.5 ppm
Cattle, Kidney and liver	2.0 ppm
Goats, kidney and liver	2.0 ppm
Hogs, kidney and liver	2.0 ppm
Horses, kidney and liver	2.0 ppm
Sheep, kidney and liver	2.0 ppm

M. Flood, 5/6/93 memo, page 5

> The new ruminant metabolism study was reviewed by S. Willett in her memo of 6/11/91 for PP#1F3974. Fifty-one percent (2.3 ppm) of the liver residue and 32% (0.84 ppm) of the kidney residue were identified. Ms. Willett concluded that "Additional characterization of residues in liver and kidney may be necessary if the residue levels in the feed items approach those used in the metabolism study... Additionally, no details on sample handling and length of storage were supplied, and no data from storage stability studies on animal commodities were submitted or referenced. This information is needed to insure sample integrity."

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EPA SERIES 361

SEP 20 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#1F3974 -- Propiconazole (Tilt®) in/on Grasses Grown for Seed. Ciba-Geigy Amendment Dated 7/2/93.

DP Barcode: D192904. CBTS # 12202.

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

THROUGH: Debra F. Edwards, Ph.D., Chief
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

TO: Sidney Jackson, PM Team 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Albin Kocialski, Section Head
Registration Section
Chemical Coordination Branch
Health Effects Division (H7509C)

In this submission, Ciba-Geigy has responded to deficiencies outlined in our 5/12/93 memo.

Conclusions (pertaining to this memo only)

1. Questions concerning sample handling and storage of samples from the ruminant metabolism study have been resolved and are discussed in our concurrent memo for PP#8F3674.

2. Recovery calculations have been adequately explained.

3. The experimental design of the crop field trials has been adequately explained.

Recommendation

TOX considerations permitting, CBTS has no objection to issuance of the proposed tolerances:

Commodity	Tolerance (ppm)
Grass Seed Screenings	60.0
Grass Hay (Straw)	40.0
Grass, Forage	0.5
Cattle, kidney and liver	2.0
Goats, kidney and liver	2.0
Hogs, kidney and liver	2.0
Horses, kidney and liver	2.0
Sheep, kidney and liver	2.0

Detailed Considerations

Deficiencies listed in our 5/12/93 memo are given with Ciba-Geigy's responses and our comments:

CBTS Deficiency #1b (Conclusion #1b from our 5/12/93 memo)

> The nature of the residue in ruminants will be understood once details of sample handling and length of storage for animal commodities have been submitted (PP#1F3974, S. Willett, memo of 6/11/191; PP#8F3674, M. Flood, memo of 5/6/93). The residue to be regulated is, tentatively, the same as for plants.

Ciba-Geigy Response

The registrant has submitted the identical response to that submitted for PP#8F3674. Our concurrent memo for that petition should be consulted.

CBTS Comment

In our concurrent memo for PP#8F3674, we concluded that the deficiency was resolved for ruminants but not poultry. Since neither grass nor grass seed is a poultry feed item, this deficiency is resolved for this petition.

CBTS Deficiency # 2b

> Recoveries associated with the residue analyses are acceptable; however the petitioner should verify the calculation of recovery from the forage control fortified with 0.1 ppm propiconazole (ABR-92070, page 37, no. 15).

Ciba-Geigy Response

The percent recovery [from the above-cited sample] was reported as 72% and not 90% because of a small peak (0.49 pg) found in the control sample run no. 14), which quantitated to 0.0195 ppm. The control amount was submtracted from the 0.091 recovery before calculating the percent recovered. In future Ciba reports, an intermediate value will be inserted into the caption line for procedural recovery samples in order to show ppm corrected for control amount.

CBTS Comment

This deficiency is resolved.

CBTS Deficiency #3

> Acceptable residue data were generated from 8 field trials....the registrant should state whether the two replicate samples from plots treated at the 1X rate refer to two composities from one treated plot or one composite each from two independently treated plots.

Ciba-Geigy Response

In three out of the eight field residue trials (OW-FR-628-91, OW-FR-629-91, OW-FR-630-91), Rep A and Rep B test plots were established as separate entities, i.e. the test material for the 1X rate treatment was independently mixed for and sprayed on test plots Rep A and Rep B. Composite samples from the Rep A and Rep B plots were collected separately and labeled appropriately.

In the other five field trials.... the test material was mixed for and sprayed on the entire 1X treatment area. The treated area was then divided to establish test plots Rep A and Rep B. Samples were collected separately from the Rep A and Rep B test plots and labeled as above.

CBTS Comment

This deficiency is resolved.

There are hardly sufficient field trials to draw conclusions from the results of the two types of experiments, but we note that the average of the relative standard deviations from average residues from the five field trials were higher with seed and seed screenings and lower with straw. In general we would expect more variability in the residues from the three field trials.

cc: RF, Circu., Mike Flood, E. Haeberer, PP#1F3974.
H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):9/20/93.
RDI:SectionHead:ETHaeberer:9/20/93:BranchSeniorScientist:RALoranger:
9/20/93.

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

MAY 17 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Propiconazole. Proposed Extension of Expiration Date for Tolerance in/on Grass Hay.

DP Barcode D191344. CB # 11882.

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

THROUGH: Elizabeth T. Haeberer, Section Chief
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

TO: Susan Lewis/Sidney Jackson, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

By FAX letter dated 5/17/93, Ciba-Geigy has requested extension of the expiration date for the tolerance for residues of propiconazole in/on grass hay. The registrant has also proposed to change the tolerance from the currently listed 5 ppm to 40 ppm, which is the proposed permanent tolerance in PP#1F3974. As for the recently proposed tolerances for grass seed screenings, forage and liver and kidney of ruminants -- see our concurrent memo -- the proposed expiration date for the tolerance on hay is January 31, 1994.

CBTS has no objection to the proposed tolerance with expiration date.

cc: RF, Circu., Mike Flood, E. Haeberer, PP#1F3974.
H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):5/17/93.
RDI:SectionHead:ETHaeberer:5/17/93:BranchSeniorScientist:RALoranger:
5/17/93.

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MAY 17 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Propiconazole. Proposed Extension of Expiration Date for Tolerance in/on Grass Seed Screenings, Hay, Forage and Animal Commodities.

DP Barcode D191329. CB # 11881

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

THROUGH: Elizabeth T. Haeberer, Section Chief
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

TO: Susan Lewis/Sidney Jackson, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

By FAX letter dated 5/14/93, Ciba-Geigy has requested extension of the expiration date for currently established tolerances for propiconazole and its formulations Tilt® Fungicide (EPA Reg. No. 100-617) and Tilt Gel Fungicide (EPA Reg. No. 100-737) with one exception. The grass seed screening tolerance would be elevated from the current 10 ppm to 60 ppm, the proposed tolerance in the petition for permanent tolerances, PP#1F3974. The following tolerances would expire January 31, 1994:

Kidney, Liver of Cattle, Goats, Hogs, Horses and Sheep	2.0 ppm
Grass, hay	5.0 ppm
Grass, forage	0.5 ppm
Grass, seed screenings	60.0 ppm

CBTS Comment

In our memo dated 5/12/93 for PP#1F3974, we stated that "CBTS has no objection to extension of the time period for the

tolerances having an expiration date provided that the tolerances are changed to those proposed in the current submission." The proposed tolerances for propiconazole in the animal commodities listed above are the current tolerances (with expiration date), and the tolerances for grass hay and forage are also the current tolerances with an expiration date. The current tolerance for seed screenings is 10 ppm. The permanent tolerances proposed in PP#1F3974 for grass hay, forage and seed screenings are, respectively, 40.0 ppm, 0.5 ppm and 60 ppm. The proposed permanent tolerances on the animal commodities are the current tolerances with expiration date. Ciba-Geigy must also propose a change in the tolerance with expiration date for hay from 5.0 ppm to 40 ppm.

We assume that omission of the tolerance change for hay was an oversight. If Ciba-Geigy proposes a tolerance of 40 ppm for hay, CBTS will have no objection to extension of the expiration date for this tolerance. As presently submitted, we have no objection to extension of the expiration date for the proposed tolerances on animal commodities, above, and the proposed tolerances on grass forage and seed screenings.

cc: RF, Circu., Mike Flood, E. Haeberer, PP#1F3974.
H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):5/17/93.
RDI:SectionHead:ETHaeberer:5/17/93:BranchSeniorScientist:RALoranger:
5/17/93.

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MAY 12 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#1F3974 -- Propiconazole (Tilt®) in/on Grasses Grown for Seed. Ciba-Geigy Amendment Dated 1/14/93.

DP Barcodes: D187417, D190147, D190263. CB #s: 11304, 11769, 11776, 11777, 11778.
MRID #s 424495-01, 426341-01 through -02.

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

Mike Flood

THROUGH: Debra F. Edwards, Ph.D., Chief
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

Debra Edwards 5/12/93

TO: Susan Lewis/S. Jackson, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Albin Kocialski, Section Head
Registration Section
Chemical Coordination Branch
Health Effects Division (H7509C)

With cover letter dated 1/14/93, Ciba-Geigy Corporation has submitted data for residues of propiconazole {1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole} and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent equivalent in/on grass seed screenings, straw (hay) and forage. The submission also includes a revised Section F and results from a market basket survey done on grass seed screening pellets.

The following tolerances are proposed:

Commodity	Tolerance (ppm)
Grass Seed Screening	60.0
Grass Hay (Straw)	40.0
Grass, Forage	0.5
Cattle, kidney and liver	2.0
Goats, kidney and liver	2.0
Hogs, kidney and liver	2.0
Horses, kidney and liver	2.0
Sheep, kidney and liver	2.0

Tolerances for animal commodities are equal to the tolerances established under 40 CFR 180.434 as a result of PP#9F3706. The current expiration date for these tolerances is 6/1/93. The tolerances have also been proposed in PP#8F3674 (for corn and pineapple).

Tolerances with an expiration date for grass hay, forage and seed screenings are, respectively, 5.0 ppm, 0.5 ppm and 10.0 ppm. These tolerances also expire 6/1/93.

In a previous submission, reviewed in S. Willett's 6/11/91 memo, tolerances on hay (straw), forage and seed screenings were proposed at 40 ppm, 2 ppm and 70 ppm, respectively. Residue data supporting these tolerances were deemed unacceptable because they did not reflect the proposed label use. Application intervals were significantly shorter than the 14 days specified on the label, and samples of seed were taken at less than the 20 day PHI. Additionally, residue levels in control samples were unacceptably high -- as high as 11 ppm.

Because the new studies show residues in excess of the temporary tolerances set for grass seed screenings and hay, Ciba-Geigy has previously submitted results in accordance with FIFRA Section 6(a)(2) by letters 8/18/92 and 11/11/92. The 6(a)(2) data were also included in the residue data submitted in PP#1F3974 and will not be discusses separately.

Summary of Deficiencies Remaining to Be Resolved

----- Nature of residue in ruminants

----- Explanation of recovery calculations

----- Explanation of crop field trial protocol

Conclusions

1a. The nature of the residue in plants is adequately understood. The residue to be regulated is parent propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid.

1b. The nature of the residue in ruminants will be understood once details of sample handling and length of storage for animal commodities have been submitted (PP#1F3974, S. Willett, memo of 6/11/91; PP#3674, M. Flood, memo of 5/6/93). The residue to be regulated is, tentatively, the same as for plants.

2a. Adequate enforcement methodology exists to quantify propiconazole and its metabolites in crops and animal commodities (PP#4F3074, PP#4F3007, PP#4E3026, memo of S. Malak, 5/28/87).

2b. Recoveries associated with the residue analyses are acceptable; however the petitioner should verify the calculation of recovery from the forage control fortified with 0.1 ppm propiconazole (ABR-92070, page 37, no. 15).

3. Acceptable residue data were generated from 8 field trials. The residue data support the proposed tolerances on grass seed screenings, hay and forage (regrowth). However, the registrant should state whether the two replicate samples from plots treated at the 1X rate refer to two composites from one treated plot or one composite each from two independently treated plots.

4. Proposed tolerances for ruminant commodities are appropriate.

5a. Anticipated residues (average residues) for grass seed screenings, hay and forage are 21 ppm, 8.8 ppm and 0.12 ppm, respectively. No percent crop treatment factor has been included.

5b. Results from a market basket survey of seed screening pellets showed a high residue value of 12.6 ppm. Three samples had residues exceeding the temporary tolerance of 10 ppm. Although seed screenings from the Pacific Northwest are commonly made into pellets, it is not clear that this is the practice in the other states for which use is possible, i.e., NE and MN; and therefore,

the results will not be used in determination of anticipated residues. Ciba-Geigy may wish to demonstrate why anticipated residues should be calculated on the basis of pellet analyses rather than from analyses of seed screenings themselves.

6. Anticipated residues in cattle are 0.007 ppm, milk; 0.46 ppm, kidney; 0.42 ppm, liver; 0.02 ppm, fat; 0.01 ppm, meat. These were determined from the cattle feeding study using anticipated residues in grass and barley. As noted in Conclusion 5a, no percent crop treatment factor was applied to the RACS contributing to the animal diets. If a DRES analysis indicates that more accurate anticipated residues should be determined, CBTS will formally request appropriate percent crop treatment factors from BEAD.

7. An International Residue Limit Status sheet is appended to this review. There is a Codex maximum residue limit of 0.05 mg/kg propiconazole, per se, in "edible offal (mammalian)", which would include kidney. It would be impossible to convert U.S. tolerances for propiconazole and metabolites to propiconazole tolerances because the residue data generated in the U.S. were obtained using an analytical method which does not distinguish between propiconazole and its metabolites.

Recommendations

CBTS recommends against establishment of the proposed permanent tolerances for reasons given in Conclusions 1b (nature of residue in ruminants); 2b (recovery calculation); and 3 (information concerning field trials).

CBTS has no objection to extension of the time period for the tolerances having an expiration date provided that the tolerances are changed to those proposed in the current submission.

Because anticipated residues in ruminants are different from those used in previous DRES calculations, CBTS recommends that a new DRES analysis be carried out.

Detailed Considerations

Proposed Use

The current label for Tilt specifies application of 4-8 fl. oz./A (maximum 4 fl. oz. on bluegrass) at 14-21 day intervals. Do not apply more than 32 fl. oz. Tilt/acre/growing season. Make the last application at least 20 days before seed matures. Do

not feed hay cut within 20 days of the last application or graze treated areas within 140 days of the last application. The label specifies application only in NE, OR, WA, ID and MN.

Tilt® Fungicide (Tilt 3.6E) contains 41.8% a.i. or 3.6 lbs ai/gallon of formulated product. Four fl. oz., therefore, contains 0.11 lb ai, or 50 grams ai.

Nature of the Residue

The nature of the residue in plants is adequately understood. The residue to be regulated is propiconazole, per se, and its metabolites determined as 2,4-dichlorobenzoic acid (PP#8F3674, C. Deyrup, memo of 12/14/88).

The nature of the residue in ruminants and poultry will be understood once details of sample handling, length of storage and storage stability data for residues of propiconazole in animal commodities have been submitted (PP#1F3974, S. Willett, memo of 6/11/91; PP#8F3674, M. Flood, 5/6/93). The residue to be regulated is tentatively the same as in plants.

Residue Data

New residue data have been submitted in the following report:

> "Magnitude of Residues of Propiconazole in or on Grasses Grown for Seed Following Application of Tilt 3.6E," J.W. Smith, 12/17/92, Lab Project ID ABR-92070. (MRID # 426341-01)

The analytical work was conducted at EPL-BIO ANALYTICAL SERVICES, Harristown, IL.

Nine field trials were held in ID, OR, MN and WA. Plots of bluegrass, bromegrass, timothygrass, fescue, and perennial ryegrass were treated with four applications of Tilt 3.6E.

Samples were taken during the 1991 growing season and maintained 7-12 months in frozen storage prior to extraction and analysis. Analyses generally followed extraction within two or three weeks, but some extracts were held for over one month. Stability of weathered propiconazole residues in extracts of corn silage and soybeans was shown for three and eight months, respectively. These data can be translated to extracts from grass commodities. The registrant states that a storage stability study for weathered residues of propiconazole in grass seed, straw and forage will run through December, 1992. A summary has been submitted as Table V of ABR-9207, in which data from a market basket survey of grass seed screening pellets are reported. (See discussion below.) The summary shows that

average (weathered) residue levels in forage, straw and seeds are higher after 25 months than initially. Available data for soybean fodder and grain (6 months) and peanut fodder, shells and nutmeats (25 months) can be translated to grass in the interim.

Residues of propiconazole and metabolites analyzed as 2,4-dichlorobenzoic acid were determined by Analytical Method AG-454B, similar to AG-454A, which has been validated by EPA. Samples are extracted by refluxing with 20% concentrated ammonium hydroxide/methanol for one hour. An aliquot is concentrated and refluxed with potassium permanganate in sodium hydroxide, which converts propiconazole and its metabolites to the 2,4-dichlorobenzoate salt. After acidification, the benzoic acid is partitioned into 10% diethylether/hexane and the organic phase taken to dryness. The acid is converted to the methyl ester with diazomethane, and the methyl ester is quantitated by capillary gas chromatography/electron capture detection. Procedural recoveries from controls fortified from 0.10 to 25 ppm averaged 93.3%±16.9% (n = 78). Submitted chromatograms show well resolved methyl ester peaks. Recoveries associated with the chromatograms can be verified -- unlike those in PP#8F3674 -- although the registrant should explain how 0.09 ppm recovered from 0.10 ppm is 72% recovery, not 90% (Forage control 1-8-A).

Residues in control samples ranged from <0.05 ppm to 0.50 ppm in seed, <0.05 ppm to 0.30 ppm in straw, <0.05 ppm to 0.36 ppm in seed screenings and <0.05 ppm to 0.11 ppm in forage (regrowth). These levels are well below the proposed tolerances and would not invalidate the residue data.

Residue data results are given in the following tables. We assume that replicate samples (A and B), from plots treated at the 1X rate, refer to two composite samples taken from the same treated plot rather than to composites from two independently treated plots. This should be confirmed.

Table 1a

Residues of Propiconazole in Grass Seed
Following Applications of Tilt 3.6E to
Grasses Grown for Seed

Field Test No./Location/Variety	Total Application Rate (grams ai/A)	PHI (Days)	Propiconazole Residue (ppm)
OW-FR-123-91 Oregon Bluegrass	200(1X)	21	9.0
	200(1X)		4.5
	400(2X)		7.0
	200(1X)	29	6.6
	200(1X)		5.2

	400(2X)		10
OW-FR-125-91 Oregon Tall Fescue	400(1X)	20	3.3
	400(1X)		2.1
	800(2X)		1.6
	400(1X)	28	2.0
	400(1X)		3.2
	800(2X)		3.6
OW-FR-628-91 Washington Fescue	400(1X	20	13
	400(1X)		12
	800(2X)		26
	400(1X)	28	9.3
	400(1X)		11
	800(2X)		27
OW-FR-629-91 Washington Bromegrass	400(1X)	20	19
	400(1X)		14
	800(2X)		22
	400(1X)	28	16
	400(1X)		17
	800(2X)		11
OW-FR-630-91 Idaho Bluegrass	200(1X)	20	2.0
	200(1X)		1.6
	400(2X)		2.7
	200(1X)	28	1.9
	200(1X)		0.85
	400(2x)		5.6
MW-FR-502-91 Minnesota Bluegrass	200(1X)	11	4.6
	200(1X)		4.8
	400(2X)		10
	200(1X)	20	4.3
	200(1X)		6.4
	400(2X)		13
MW-FR-503-91 Minnesota Ryegrass	400(1X)	20	21
	400(1X)		23
	400(1X)	28	7.6
	400(1X)		5.8

MW-FR-504-91 Minnesota Timothygrass	400(1X)	20	1.2
	400(1X)		1.2
	400(1X)	28	0.52
	400(1X)	28	0.57

Table 1b

Residues of Propiconazole in Grass Straw Following Applications of Tilt 3.6E to Grasses Grown for Seed

Field Test No./Location/Variety	Total Application Rate (grams ai/A)	PHI (Days)	Propiconazole Residue (ppm)
OW-FR-123-91 Oregon Bluegrass	200(1X)	21	5.3
	200(1X)		6.1
	400(2X)		8.8
	200(1X)	29	3.5
	200(1X)		4.8
	400(2X)		4.9
OW-FR-125-91 Oregon Tall Fescue	400(1X)	20	1.4
	400(1X)		2.4
	800(2X)		5.9
	400(1X)	28	1.5
	400(1X)		2.6
	800(2X)		3.4
OW-FR-628-91 Washington Fescue	400(1X)	20	16
	400(1X)		9.4
	800(2X)		11
	400(1X)	28	3.6
	400(1X)		2.3
	800(2X)		21
OW-FR-629-91 Washington Bromegrass	400(1X)	20	36
	400(1X)		28
	800(2X)		43
	400(1X)	28	23
	400(1X)		17
	800(2X)		17

OW-FR-630-91 Idaho Bluegrass	200(1X)	20	3.0
	200(1X)		3.3
	400(2X)		2.5
	200(1X)	28	2.8
	200(1X)		2.9
	400(2X)		6.0
MW-FR-502-91 Minnesota Bluegrass	200(1X)	11	2.1
	200(1X)		1.7
	400(2X)		3.2
	200(1X)	20	1.8
	200(1X)		2.1
	400(2X)		3.7
MW-FR-503-91 Minnesota Ryegrass	400(1X)	20	15
	400(1X)		14
	400(1X)	28	11
	400(1X)		16
MW-FR-504-91 Minnesota Timothygrass	400(1X)	20	13
	400(1X)		13
	400(1X)	28	5.8
	400(1X)		7.9

Table 1c

Residues of Propiconazole in Grass Seed Screenings Following Applications of Tilt 3.6E to Grasses Grown for Seed

Field Test No./Location/Variety	Total Application Rate (grams ai/A)	PHI (Days)	Propiconazole Residue (ppm)
OW-FR-123-91 Oregon Bluegrass	200(1X)	21	8.4
	200(1X)		8.5
	400(2X)		15
	200(1X)	29	15
	200(1X)		12
	400(2X)		12
OW-FR-125-91 Oregon Tall Fescue	400(1X)	20	6.9
	400(1X)		9.3
	800(2X)		13

	400(1X)	28	2.6
	400(1X)		6.6
	800(2X)		6.6
OW-FR-628-91 Washington Fescue	400(1X)	20	19
	400(1X)		22
	800(2X)		25
	400(1X)	28	12
	400(1X)		11
	800(2X)		21
OW-FR-629-91 Washington Bromegrass	400(1X)	20	41
	400(1X)		35
	800(2X)		62
	400(1X)	28	11
	400(1X)		13
	800(2X)		18
OW-FR-630-91 Idaho Bluegrass	200(1X)	20	2.2
	200(1X)		2.1
	400(2X)		3.0
	200(1X)	28	2.1
	200(1X)		3.7
	400(2X)		4.4
MW-FR-502-91 Minnesota Bluegrass	200(1X)	11	3.7
	200(1X)		5.9
	400(2X)		12
	200(1X)	20	2.9
	200(1X)		7.3
	400(2X)		9.3
MW-FR-503-91 Minnesota Ryegrass	400(1X)	20	43
	400(1X)		38
	400(1X)	28	35
	400(1X)		38
MW-FR-504-91 Minnesota Timothygrass	400(1X)	20	39
	400(1X)		52
	400(1X)	28	36
	400(1X)		30

Table 1d

Residues of Propiconazole in Grass Forage Following Applications of Tilt 3.6E to Grasses Grown for Seed

Field Test No./Location/Variety	Total Application Rate (grams ai/A)	PHI (Days)	Propiconazole Residue (ppm)
OW-FR-123-91 Oregon Bluegrass	200(1X)	140	0.07,0.06
	200(1X)		0.07,0.11
	400(2X)		0.18,0.10
OW-FR-125-91 Oregon Tall Fescue	400(1X)	140	0.31
	400(1X)		0.28
	800(2X)		0.37
OW-FR-628-91 Washington Fescue	400(1X)	140	<0.05
	400(1X)		<0.05
	800(2X)		<0.05
OW-FR-630-91 Idaho Bluegrass	200(1X)	140	<0.05
	200(1X)		<0.05
	400(2X)		<0.05

These data support the proposed tolerances on seed screenings, hay and forage.

Anticipated Residues

Average Residues (reflecting 1X use rates and PHI 20-21 days) for seed screenings, hay and forage are, respectively, 21.0±17.7 ppm, 8.8±9.7 ppm and 0.12±0.12 ppm. Data reviewed in S. Willett's 6/11/91 memo were obtained at lower PHI's and short application intervals and were not used in calculating the averages. Earlier data, reviewed by H. Fonouni in his memo of 2/7/89 (PP#9F3706), contained only one data point for seed screenings (chaff) at PHI 28 days and was not used in calculation of the average residue. Results from two field trials could be used in calculating the average for hay -- 8624/Oregon, 0.8 ppm (from maximum total application 200 g ai/A on bluegrass with PHI 22 days), and 8626/Oregon, 2.5 ppm (from maximum total application 400 g ai/A on ryegrass with PHI 20 days).

Grass Seed Screening Pellets (GSSP's) were analyzed in a market basket survey. According to Ciba-Geigy, in commercial practice, unprocessed grass seed screenings are not fed directly to livestock; rather, they are blended with screenings from

untreated grass seed, straw and waste seeds from grasses, sugarbeets, etc. and pelletized. The following report has been submitted:

> "Propiconazole Magnitude of the Residue in or on Grass Seed Screening Pellets Obtained from Market Basket Samplings," R.E.M. Wurz, 1/5/93, Lab Project ID ABR-92071. (MRID # 426341-02) Analyses were conducted at Ciba-Geigy's laboratory in Greensboro, NC.

GSSP samples were taken on a monthly basis from three commercial processors in Oregon from mid-November, 1991 to mid-October, 1992. Two replicate samples were randomly collected from current pellet production bins and sent frozen to Greensboro, NC. where they were placed under frozen storage. Samples were analyzed from <1 mo. to 8 mo. after sampling. Pellets were analyzed by Analytical Method AG-454B with some minor modifications. Because there were no untreated control samples -- all analyzed samples contained residues >0.5 ppm -- the lowest fortification level analyzed was 1.0 ppm.. Recoveries, corrected for levels found in the unfortified samples, averaged 80±8%.

Residues found varied from 0.47 ppm to 12.6 ppm with an average of 4.1 ppm. Average residues for each of the three field tests (30 samples for each test, including replicate samples) were 6.48±3.17 ppm, 2.85±2.06 ppm and 3.11±2.67 ppm. Residues were found in all samples. Three samples from Field Test #0W-MB-101-92 contained residues which exceed the temporary tolerance of 10 ppm.

Comment

The use of grass seed screenings in animal feed was addressed in a memo from Joseph A. Ferrante, BEAD, to Chuck Trichilo dated 1/10/89 (PP#9F3706). According to the memo, almost all of the seed screenings (99%) from the Pacific Northwest are pelletized for cattle feed. The remaining 1 percent is used as mulch. The Pacific Northwest accounts for up to 70% of the national grass seed production.

Although seed screenings are pelletized in the Pacific Northwest, this practice is apparently not followed in Nebraska or Minnesota. We therefore prefer to use the average residue value of 21 ppm for seed screenings in estimation of residues in meat and milk. Ciba-Geigy may wish to present arguments as to why its market basket survey results are more appropriate.

Although complete information is not available, W.H. Kosesan, Oregon Department of Agriculture, in a 11/30/88 letter addressed To D. Stubbs, EPA, has estimated that grass seed screenings may comprise up to 25% of the diet of dairy cattle and

up to 30% of the diet of beef cattle. These percentages will be used in our calculations.

Meat, Milk, Poultry and Eggs

Tolerances. In our concurrent memo for PP#8F3674, worst case diets for beef and dairy cattle were estimated using a diet consisting of grass seed screenings, corn forage and corn grain. Proposed tolerances for these commodities are 60 ppm, 12 ppm and 0.1 ppm, respectively. Corn forage/silage can constitute up to 30% of the diet of beef cattle and 50% of the diet of dairy cattle. Respective percentages for corn grain are 80% and 50%. Maximum percentages for grass seed screenings and corn forage were used to estimate the maximum residues. We conclude that proposed tolerances of 2.0 ppm for kidney and liver, 0.1 ppm for fat and meat, and 0.05 ppm for milk are appropriate. Note that propiconazole is not currently registered for use in/on corn. A diet consisting of grass commodities and other registered crops would produce lower estimated concentrations in animal commodities.

Anticipated Residues.

1. Including Corn Forage in the Diet. The anticipated residue (AR) for corn forage can be determined by averaging the residue values for that rac given in Table X, Report ABR-88054 (MRID # 407833-03) in PP#8F3674. Because most of the residue values were obtained using a seasonal maximum of 175 g ai/A rather than the maximum 200 g ai/A, residue values reflecting the lower dosage have been multiplied by 1.14. The average for forage is determined to be 2.65±2.30 ppm. Corn forage consists of about 25% dry matter. Therefore, on a dry weight basis the level for forage is 10.4 ppm, which will be used in determination of meat and milk AR's. Using 21 ppm as the AR for grass seed screenings, the AR's in meat and milk can be determined as shown in Tables 2a and 2b.

Table 2a

Diet for Beef and Dairy Cattle Based on Anticipated Residues of Propiconazole in Grass Seed Screenings and Corn

COMMODITY	ANTICIPATED RESIDUE (PPM)	% DIET	DIET PPM
Beef Cattle			
Grass, screenings	21	30	6.3
Corn Forage	10.4	30	3.12
Corn Grain	0.05	40	0.02
		Total	**9.4 ppm**
Dairy Cattle			
Grass, screenings	21	25	5.25
Corn Forage	10.4	50	5.2
Corn Grain	0.05	25	0.01
		Total	**10.4 ppm**

Table 2b

Anticipated Residues in Cattle Determined from a Diet Including Corn

Cattle Sample	Residue @ 75 ppm	Anticipated Residue (ppm)
Milk	0.08	0.01
Kidney	4.7	0.59
Liver	4.3	0.54
Fat	0.23	0.03
Meat	0.11	0.01

The feeding level of 75 ppm was used rather than 15 ppm because measurable residues in fat, meat and milk were found from the higher dose level.

Note that corrections have <u>not</u> been made for percent crop

treated. Should such information be useful for a DRES analysis, a formal request will be made to BEAD.

2. Excluding Corn Forage in the Diet. Because the petition for use of propiconazole in/on corn is still active, a DRES analysis necessary for extension of the tolerance expiration date for grass grown for seed should use AR's determined only with currently registered commodities. One such diet (Debra Edwards, memo of 5/23/89) would be that shown in Table 3a. The average value for grass forage was converted to dry weight basis by dividing by 0.3.

Table 3a

Diet for Beef and Dairy Cattle Based on Anticipated Residues of Propiconazole in Grass Seed Screenings, Hay and Barley Grain

COMMODITY	ANTICIPATED RESIDUE (PPM)	% DIET	DIET PPM
Beef Cattle			
Grass, screenings	21	30	6.3
Grass, hay	8.8	10	0.88
Grass, forage	0.40	40	0.16
Barley, grain	0.05	20	0.01
		Total	**7.4 ppm**
Dairy Cattle			
Grass, screenings	21	25	5.25
Grass, Hay	8.8	10	0.88
Grass, forage	0.40	65%	0.26
		Total	**6.4 ppm**

Table 3b

Anticipated Residues in Cattle Determined from a Diet Including Grass and Barley

Cattle Sample	Residue @ 75 ppm	Anticipated Residue (ppm)
Milk	0.08	0.007
Kidney	4.7	0.46
Liver	4.3	0.42
Fat	0.23	0.02
Meat	0.11	0.01

Because these levels are significantly different from those used in earlier calculations, CBTS recommends that a new DRES analysis be carried out using the values given in Table 3b. Percent crop treated has not been included. [Our memo of 5/23/89 (D.Edwards) did include percent crop treated.]

Other Considerations

An International Residue Limit Status sheet is appended to this review. There is a Codex maximum residue limit of 0.05 mg/kg propiconazole, per se, in "edible offal (mammalian)", which would include kidney. It would be impossible to convert U.S. tolerances for propiconazole and metabolites to propiconazole tolerances because the residue data generated in the U.S. were obtained using an analytical method which does not distinguish between propiconazole and its metabolites.

Attachment: International Residue Limit Status sheet

cc: RF, Circu., Mike Flood, E. Haeberer, PP#1F3974, PP#8F3674.

H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):5/12/93.
RDI:SectionHead:ETHaeberer:5/11/93:BranchSeniorScientist:RALoranger:
5/11/93.

Attachment

J. Hetes 5/10/93

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Propiconazole

CODEX NO. 160

CODEX STATUS:

/7 No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Propiconazole per se

Crop(s)	Limit (mg/kg)
edible offal (mammalian)	0.05

PROPOSED U.S. TOLERANCES:

Petition No. 1F3974

RCB Reviewer F Loeb

Residue: Propiconazole + metabolites ~~con~~ analyzed as 2,4-dichlorobenzoic acid

Crop(s)	Limit (mg/kg)
Grass, seed screenings	60
hay (straw)	40
forage	0.5
Cattle, goats, hogs, horses, sheep kidney and liver	2

CANADIAN LIMITS:

/✓ No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

/✓ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES:

Form revised 1986

End of Document

1150 0 # 3974 PC 122101

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MAY 6 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#8F3674 -- Propiconazole (Tilt®) in/on Corn and Pineapple. Ciba-Geigy Amendment Dated 11/20/92.

DP Barcode: D185251. CB # 10974.
MRID # 425640-04 through -06.

FROM: Michael T. Flood, Ph.D., Chemist
Tolerance Petition Section II
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

Mike Flood

THROUGH: Debra F. Edwards, Ph.D., Chief
Chemistry Branch I -- Tolerance Support
Health Effects Division (H7509C)

Debra Edwards

TO: Susan Lewis/S. Jackson, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

The present submission addresses deficiencies outlined in CBTS' 12/14/88 memo (C. Deyrup). Ciba-Geigy is withdrawing its requests for tolerances on legume vegetables and foliage and is proposing the following tolerances for residues of the fungicide propiconazole (1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-1H-1,2,4-triazole) and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as parent equivalents:

Commodity	Proposed Tolerance (ppm)
Corn forage	12.0
Corn fodder	12.0
Corn grain	0.1
Corn, Sweet (K+CWHR)	0.1
Cattle, kidney & liver	2.0
Goats, kidney & liver	2.0
Hogs, kidney & liver	2.0

Sheep, kidney & liver	2.0
Pineapples	0.1
Pineapple fodder	0.1

Tolerances for corn forage and fodder had been previously proposed as 10 ppm. The tolerances on animal commodities are the current tolerances with an expiration date established under 40 CFR 180.434 as a result of PP#9F3706. The current expiration date for these tolerances is 6/21/93.

Summary of Deficiencies Remaining to Be Resolved

----- Metabolism (information on storage)

----- Processed Fractions (storage stability, examples of recovery calculations)

Conclusions

1a. The nature of the residue in plants is adequately understood. The residue to be regulated is propiconazole, per se, and its metabolites determined as 2,4-dichlorobenzoic acid.

1b. The nature of the residue in ruminants and poultry will be understood once details of sample handling and length of storage for animal commodities have been submitted (PP#1F3974, S. Willett, memo of 6/11/91). The residue to be regulated is, tentatively, parent propiconazole and its metabolites analyzed as 2,4-dichlorobenzoic acid.

2. Adequate enforcement methodology now exists to quantify propiconazole and its metabolites in crops and animal commodities (PP#4F3074, PP#4F3007, PP#4E3026, memo of S. Malak, 5/28/87).

3. Proposed Section 408 tolerances are appropriate.

4a. There are no storage stability data for residues of propiconazole and its metabolites in/on corn processed products (or any processed products). Stability in representative processed commodities should be demonstrated for periods up to 30 months. We suggest flour and refined oil.

4b. Examples of calculations used to determine percent recoveries in corn processed fractions should be

submitted. See our comments on page 11 of this memo.

4c. Pending adequate response to deficiencies noted in the previous two conclusions, the processing studies are acceptable. The tolerance for field corn grain will not be exceeded by residues in any processed corn fraction.

5. Proposed tolerances for ruminant commodities are appropriate. The main dietary input for propiconazole in ruminants is from grass seed screenings (PP#1F3974). Measurable residues in poultry are not predicted from the proposed uses.

Recommendation

CBTS recommends against the proposed tolerances for reasons given in Conclusions 1b (nature of the residue in ruminants) and 4a and b (processed commodities).

Detailed Considerations

Deficiencies listed in C. Deyrup's 12/14/88 memo are listed with Ciba-Geigy's response and CBTS' comments. Because the registrant is withdrawing its proposed tolerances on legume vegetables, those conclusions/deficiencies pertaining to these racs in the 12/14/88 memo will not be listed.

CBTS Deficiency # 1b (Conclusion # 1b from our 12/14/88 memo)

The petitioner will need to submit a revised label in which a treatment to foraging period is specified for... corn forage. This interval should be supported by residue data.

Ciba-Geigy Response

A revised Section B has been submitted which specifies a treatment to grazing interval of 14 days for sweet corn and 30 days for field corn. The remainder of the label for corn is unchanged from that summarized in CBTS' earlier memo.

CBTS Comment

This part of the deficiency is resolved. Submitted residue data will be summarized below.

CBTS Deficiency #1c

The petitioner should submit a revised Section B/label in which the temperature is given in degrees Fahrenheit for the use in Hawaii.

Ciba-Geigy Response

A revised Section B has been submitted which specifies the temperature in degrees Fahrenheit for the dip treatment use. The remainder of the label for pineapple is unchanged from that summarized in CBTS' earlier memo.

CBTS Deficiency # 2b

> The metabolic picture exhibited by ruminants is markedly different from that found in plants; in ruminants, there is extensive cleavage of the bridge connecting the triazole and phenyl rings. The olefin and the ketone, which are determined by the enforcement method, account for about 20% of the total radioactive residue (TRR) in milk and liver upon treatment with sulfuric acid. [CBTS] is concerned that other residues of toxicological concern, such as chlorophenols, may occur.
>
> The proposed use will substantially increase the dietary burden to at least 6.25 ppm and possibly to 9-10 ppm.
>
> [CBTS] concludes that the nature of the residue in ruminants is not adequately understood for the proposed use. The petitioner needs to more adequately account for residues containing the phenyl ring.

Ciba-Geigy Response

Ciba-Geigy submitted a new goat metabolism study in support of PP# 1F3974. Two goats received a daily dose of 125 mg phenyl ^{14}C-propiconazole for four consecutive days, equivalent to 67-92 ppm in feed.....

Ciba-Geigy has developed residue data to support the use of propiconazole on grasses grown for seed, peanuts, and legume vegetables. Based on residue data for these crops, it is expected that an extreme worst case diet for cattle would contain up to 21 ppm propiconazole residues. This level of residue would still correspond to a dietary intake for which metabolite identification in goat kidney and liver is adequate. This is further supported by method validation data...In the validation study of Method AG-517, for the determination of total propiconazole residues in meat, milk and eggs, accountability of total radioactivity derived from ^{14}C-propiconazole residues in goat and poultry tissues, milk and eggs ranged from 74-111%. This demonstrated that the majority of residues of concern (those containing the 2,4-dichlorophenyl moiety) are accounted for by the accepted enforcement methodology.

Submitted in this petition is an addendum to the goat metabolism study ("Addendum 1 to Final Report," A.M. Doweyko, MRID # 425640-06). HPLC chromatograms taken from the day 4 urine (stored frozen) from one goat are shown from 8/30/89, 12/5/89 and 4/10/90.d No qualitative change in the urine profiles could be seen.

CBTS Comment

The new ruminant metabolism study was reviewed by S. Willett in her memo of 6/11/91 for PP#1F3974. Fifty-one percent (2.3 ppm) of the liver residue and 32% (0.84 ppm) of the kidney residue were identified. Ms. Willett concluded that "Additional characterization of residues in liver and kidney may be necessary if the residue levels in the feed items approach those used in the metabolism study...Additionally, no details on sample handling and length of storage were supplied, and no data from storage stability studies on animal commodities were submitted or referenced. This information is needed to insure sample integrity."

We tentatively conclude that the nature of the residue in ruminants is propiconazole and its metabolites analyzed as 2,4-dichlorobenzoic acid. However, storage stability considerations remain outstanding, so this deficiency is not resolved. The metabolism study addendum is useful is this regard, but data on sample handling and length of storage are not present. (We note that in its 7/13/90 Phase 3 response, Ciba-Geigy states that milk and tissue samples from the cattle feeding study were frozen immediately and stored frozen at approximately -15°C for 1 to 2 months until extraction and analysis.)

CBTS Deficiency # 2c

The proposed use will result in residues of Tilt on poultry feed items. Until this proposed use, no detectable residues of Tilt had actually been found on poultry feed items. Now that real residues of Tilt are expected to arise on soybeans, a poultry study is needed. The label should be in the phenyl ring, since TOX has concluded that triazole moieties arising from Tilt are not of concern.

Ciba-Geigy Response

Ciba-Geigy submitted a new chicken metabolism study...in support of PP#1F3974...None of the poultry feed items derived from corn contain propiconazole residues, our request for a tolerance in soybeans (legume vegetables) is being withdrawn, and no poultry feed items are derived from pineapples. Therefore this conclusion does not affect the proposed use of propiconazole on corn or pineapples.

CBTS Comment

The poultry metabolism study was reviewed by S. Willett in her memo of 1/11/91 for PP#1F3974. She concluded that "The poultry metabolism study is generally acceptable. However, CBTS will withhold its final conclusions on the adequacy of the study until it can be considered in the context of the petitions to which it is relevant (i.e. tolerance petitions on corn and peanuts)." As in the ruminant study, questions were raised concerning storage stability of the metabolism samples.

So long as residues of propiconazole in corn grain remain negligible, a poultry feeding study will not be necessary to support this petition. The nature of the residue in poultry is tentatively understood. The residue to be regulated is propiconazole and its metabolites analyzed as 2,4-dichlorobenzoic acid. However, questions concerning the metabolism study must be resolved, i.e., details of sample handling and length of storage should be supplied with some data on storage stability in animal commodities. This deficiency remains. (In its Phase 3 response, dated 7/13/90, Ciba-Geigy reported that egg and tissue samples were frozen immediately and stored frozen at approximately -15°C for 3 to 4 months until extraction and analysis.)

CBTS Deficiency # 3b

> [CBTS] has questioned the adequacy of the ruminant metabolism studies. No poultry metabolism study has been submitted for review. Therefore, at this time [CBTS] can make no judgment on the ability of the analytical methodology to determine the residues of concern.

Ciba-Geigy Response

EPA has since determined that the analytical methodology for ruminants and poultry is adequate for enforcement purposes as described in EPA's review of PP#1F3974....

CBTS Comment

S. Willett concluded in her 6/11/91 memo for PP#1F3974 that the enforcement methodology for crops and animal commodities was capable of quantifying propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety. This deficiency is resolved.

CBTS Deficiency # 4

> The petitioner needs to submit data to support the stability of the extracts, which could be strongly basic. The extracts were stored up to 4 months at some unspecified temperature. Without storage stability data on the extracts, DEB cannot judge the adequacy of the residue data on pineapples, celery, corn, legume vegetables, and the foliage of legume vegetables.

Ciba-Geigy Response

An extract storage stability study was conducted and results were reported in ABR-90017....

CBTS Comment

The study (MRID # 414868-02) was reviewed by W.T. Chin (PP#0F3869, memo of 8/15/90). The reviewer concluded that propiconazole residues in extracts of silage-stage corn forage and soybeans are stable for at least 3 and 8 months, respectively, when stored at 4°C. This deficiency is resolved.

CBTS Deficiency # 5a

> The petitioner will need to submit the standard curves which were used to generate the residue data for those commodities in which significant levels of propiconazole were found (corn forage and fodder, celery, legume vegetable foliage) in order to demonstrate the linearity of the detector response.

Ciba-Geigy Response

Standard curve data and resulting standard curves for the 2,4-dichlorobenzoic acid methyl ester standards injected with the corn forage and fodder samples reported in ABR-88054 are provided in Figures 1 to 43. These standards were injected with each set of corn residue samples such that residue samples were always bracketed with standard injections. Each analytical set of residue samples, as a rule, began and ended with a standard injection, and one standard was injected between each one to three residue samples. A linear regression calibration curve was then constructed for the analytical set....

CBTS Comment

The submitted calibration curves show that detector response is basically linear, although the data were best fit using a second order curve. Data points tagged as "outliers" were always used in constructing the standard curves. This deficiency is resolved.

CBTS Deficiency #5j

> A residue level of 9.30 ppm in corn forage was reported from a field corn trial with a PHI or 27 days. If the value of 9.30 ppm is corrected for the total dosage permitted (a factor of 200/175), the proposed tolerance of 10.0 ppm would not be adequate. Aside from the dosage consideration, the variation in recovery from forage and fodder, 71-125%, leads [CBTS] to the conclusion that the proposed tolerance on corn forage is not adequate.

Ciba-Geigy Response

Adjusting the residue level of 9.30 ppm at 175 g ai/A to the maximum application level of 200 g. ai/A the residue would become 10.6 ppm. A revised Section F has been submitted in which the tolerance for corn forage and fodder is 12.0 ppm.

CBTS Comment

This deficiency is resolved.

CBTS Deficiency #5k

> No treatment to grazing interval was specified on the label for the proposed use on corn. Given the tendency of propiconazole residues to increase with shorter PHI's, [CBTS] concludes that the available data do not support a treatment to grazing interval of less than about 30 days for field corn and 14 days for sweet corn forage. If the petitioner wishes to impose shorter treatment to grazing intervals, the corresponding residue data on corn forage would need to be submitted from the major corn-growing areas of the country.

Ciba-Geigy Response

Revised labeling which specifies a treatment-to-grazing interval of 30 days for field corn and 14 days for sweet corn is included in the revised Section B for PP#8F3674 submitted with this study.

CBTS Comment

The proposed label change was noted previously in this memo. This deficiency is resolved.

CBTS Deficiency # 5l

Before [CBTS] can estimate tolerances on forage and fodder arising from the proposed use, residue data are needed on field and sweet corn grown in CA and subjected to furrow irrigation. The data on corn foliage should reflect the petitioner's intended treatment to grazing interval.

Ciba-Geigy Response

The two California field tests reported in the original petition, one each for field corn and sweet corn, were both conducted using furrow irrigation. Updated reports for these tests, AG-A-8459 and AG-A-8304 are submitted with this report and describe the irrigation practices used...

CBTS Comment

This deficiency is resolved. We note that residues in grain, forage and fodder were not unusually different from corresponding residues found from other trials.

CBTS Deficiency # 5m

At this time, pending the review of the standard curves used to generate the residue data and residue data from furrow-irrigated corn grown in CA, [CBTS] cannot judge the adequacy of the proposed tolerances on corn grain, sweet corn, and corn fodder.

CBTS Comment

As noted above, these deficiencies have been resolved. Proposed tolerances are appropriate.

CBTS Deficiency # 6a

The petitioner has not described the soybean and corn processing studies. A detailed description of the processing studies should be submitted so that [CBTS] can determine whether common commercial practices were followed. The description should include the temperatures used during the various steps and the duration of these periods.

CBTS Deficiency # 6b

The petitioner will need to submit residue data from a corn wet milling processing study.

Residue data from the wet milling study should cover the fractions which travel through commercial channels, namely: starch, crude and refined oils, corn bran, and the feed co-products derived from wet milling. The four major feed products arising from wet milling are gluten feed, corn germ meal,

gluten meal, and condensed fermented corn extractives (steepwater).

CBTS Deficiency # 6c

At this time DEB cannot judge whether food additive tolerances are needed.

Ciba-Geigy Response

A description of the corn grain processing study is included in a letter dated 5/2/89 to Ciba-Geigy from the Food Protein Research and Development Center, Texas A & M University. This study, which included only dry milling, was conducted in a manner similar to commercial practice except for the milling procedure. Ciba-Geigy has since conducted a new corn grain processing study, which included both wet and dry milling.

CBTS Comment

Because the submitted dry milling processing study did not adequately simulate the production of corn milling fractions, that part of the study is invalid.

Ciba-Geigy has submitted new processing data in the following report:

"Magnitude of Residues of Propiconazole in Field Corn Forage and Grain and Processed Fractions Following Application of Tilt 3.6E Formulation to Field Corn," P.J. Manuli, 9/29/92, Lab. Project ID ABR-92047. (MRID # 425640-05)

Two corn field trials were conducted with Tilt 3.6E at 1X, 3X, and 5X the proposed rate. Insufficient corn grain sample was available from one of the trials, held in MS. Sufficient grain samples were obtained from the other field trial, held in IL, but in this test the last application was made at 60% silking, which is later than that allowed by the proposed label.

Harvested grain and forage were stored frozen for 29-32 months before analysis. Processing was done 2-3 months after sampling. Processed fractions were analyzed at the same time as were the racs. Storage stability data are available for peanut fodder, shells and nutmeat for 25 months. A storage stability study for incurred residues of propiconazole in grass seed, straw, and forage is in progress and will be continued for at least three and one-half years. Residues are reportedly stable through seventeen months. Additional data are necessary for processed commodities. Stability in representative processed commodities should be demonstrated for periods up to 30 months. We suggest flour and refined oil.

Residues of propiconazole and metabolites containing the 2,4-dichlorobenzyl moiety were determined by Analytical Method

AG-454B, which is essentially AG-454A, the regulatory enforcement method. Samples are extracted by refluxing with 20% concentrated ammonium hydroxide/methanol for one hour. An aliquot is concentrated and refluxed with potassium permanganate in sodium hydroxide to convert propiconazole and its metabolites to the 2,4-dichlorobenzoate salt. After acidification, the benzoic acid is partitioned into 10% diethyl ether/hexane and the organic phase taken to dryness. The acid is converted to the methyl ester with diazomethane and the methyl ester quantitated by capillary gas chromatography/electron capture detection. Recoveries from various processed corn commodities are given in the next table. The residue detected is 2,4-dichlorobenzoic acid methyl ester and converted to propiconazole equivalents using the factor 1.79.

Table 1

Recoveries of Propiconazole from Fortified Controls of Field Corn Grain Processed Fractions

Fraction	ppm Added	Percent Recovery
Dry Milling Fractions		
Whole Kernels	0.05	120
Large Grits	0.20	117
Small Grits	0.10	112
Meal	0.20	111
Flour	0.05	106
Crude Oil (Expeller)	0.50	101
Presscake (Solvent-Extracted)	0.10	71
Crude Oil (Solvent-Extracted)	0.20	68
Refined Oil	0.05	95
Wet Milling Fractions		
Whole Kernels	0.05	83
Steepwater Concentrate	0.10	81
Coarse Gluten Starch	0.20	103
Hulls	0.05	75
Gluten	0.50	101
Starch	0.20	101

Crude Oil (Expeller)	0.50	77
Presscake (Solvent-Extracted)	0.05	78
Crude Oil (Solvent-Extracted)	0.20	80
Refined Oil	0.10	61

Representative chromatograms from the various processed fractions are given. The petitioner should submit sample calculations which demonstrate how the recoveries in the previous table were calculated. For example, on page 54 (chromatograms from crude oil), No. 79, control + 0.2 ppm propiconazole -- 68 µg injected, 6.8 pg found, 0.1607 ppm; on page 55 (chromatograms from refined oil), No. 83, control + 0.1 ppm propiconazole -- 68 µg injected, 6.7 pg found, 0.0612 ppm. If identical quantities of extract are injected and the same quantity of analyte found, the concentrations should be identical, unless there has been some dilution factor.

Residues on the RACs from the two field trials are given in the following table. As noted, only the grain from the second trial was processed.

Table 2

Propiconazole Residues in Forage and Grain from Treatment at 1X, 3X and 5X with Tilt® 3.6E

State	RAC	Rate (lbs. ai/A)	PPM Propiconazole Equivalents
MS	Forage	0	<0.05
		50	1.6
		50	0.82
		150	0.53
		250	1.9
	Grain	0, 50, 50, 150, 250	<0.05
IL	Forage	0	<0.05
		50	0.24
		50	4.4
		150	12.2

		250	17.5
	Grain	0	<0.05
		50	<0.05
		50	<0.05
		150	<0.05
		150	<0.05
		250	0.07
		250	0.08

* Four applications were made at these levels.

Dry Milling Processed Fractions

A description of the dry milling process is given in pp 82-83 of the report. Oil was refined by addition of NaOH, mixing at room temperature followed by settling at 60-65°C for one hour. The oil solution was refrigerated overnight and the precipitated soapstock removed. The refined oil was further bleached and deodorized, but these fractions were apparently not analyzed.

Propiconazole residues were non-detected (<0.05 ppm) in all controls and processed fractions from corn treated at 1X. Residues were detected in certain processed fractions from corn treated at 3X: meal, 0.06 ppm; flour, 0.06 ppm; and presscake (solvent extracted), 0.05 ppm. Residues found in grain and processed fractions from corn treated at 5X are given in the following table:

Table 3

Propiconazole Residues in Field Corn Grain and Dried Milled Processed Fractions from Treatment with Tilt® 3.6E at 5X

Commodity	Residue Found (ppm Propiconazole Equivalents)
Whole Kernels	0.06
Large Grits	0.05
Small Grits	0.08
Meal	0.08
Flour	0.08
Crude Oil (Expeller)	<0.05
Presscake (Solvent Extracted)	0.08
Crude Oil (Solvent Extracted)	<0.05
Refined Oil	<0.05

Processed dry milling fractions required by our Residue Chemistry Guidelines to be analyzed are grits, meal, flour, crude and refined oil.

Wet Milling Processed Fractions

The wet milling process is described on pp 84-87. Propiconazole residues were non-detected (<0.05 ppm) in controls and all processed fractions from corn treated at the 1X rate except hulls, where 0.09 ppm was observed. Residues were found in the following processed fractions from corn treated at 3X: coarse gluten starch, 0.06 ppm; hulls, 0.20 ppm; presscake (solvent extracted, 0.07 ppm). Residues found in grain and processed fractions from corn treated at 5X are given in the following table:

Table 4

Propiconazole Residues in Field Corn Grain and Wet Milled Processed Fractions from Treatment with Tilt® 3.6E at 5X

Commodity	Residue Found (ppm Propiconazole Equivalents)
Whole Kernels	0.07
Steepwater Concentrate	<0.05
Coarse Gluten Starch	0.09
Hulls	0.22
Gluten	<0.05
Starch	<0.05
Crude Oil (Expeller)	0.07
Presscake (Solvent Extracted)	0.09
Crude Oil (Solvent Extracted)	<0.05
Refined Oil	<0.05

Processed commodities required by our Guidelines to be analyzed are starch, crude oil and refined oil.

Comment

No concentration was observed in the (required) processed fractions obtained from the wet milling process.

Apparent concentration was observed in grits, meal and flour from dried-milled processed corn, but because the reported values are close to the quantitation limit of 0.05 ppm, it is not clear whether the observed values in processed fractions are significantly different from that in grain. Additionally, the registrant claims that the only reason residues were observed in/on grain in the first place was that the corn was treated after silking -- contrary to label instructions.

Because of analytical uncertainties and the fact that measurable residues in grain are not expected when Tilt® is applied according to the label, food additive tolerances are not warranted. The proposed tolerance of 0.1 ppm in/on grain will not be exceeded by concentrations in processed commodities. However, if the label is ever changed to permit applications such that measurable residues in/on grain are expected, this subject

may have to be revisited and additional processing studies carried out.

CBTS Deficiency #7

> At a minimum, DEB can conclude that the residues in the liver and kidney of cattle, goats, hogs, horses, and sheep from the proposed uses will exceed the established 0.2 ppm tolerances. However, because the nature of the residue in animals is not adequately understood, DEB is unable to judge the adequacy of the established tolerances for meat, milk, poultry and eggs or to recommend tolerances to cover the proposed uses.

Ciba-Geigy Response

Ciba-Geigy has assumed an "extreme worst case" diet using proposed tolerances for grass seed screenings (PP#1F3974), corn forage and corn grain. The following diets are calculated for beef and dairy cattle:

Table 5a

Worst Case Diet for Beef Cattle

Commodity	Tolerance (ppm)	% Diet	Diet (ppm)
Grass, screenings	60	30*	18
Corn Forage	48**	30	14
Corn Grain	0.1	40	0.04
		TOTAL	32

* Ciba-Geigy's calculation included 20% contribution from grass seed screenings and a 50% contribution from grain. We have modified the dietary estimate so that the contribution of grass seed screenings is 30%. This point is discussed in our concurrent memo for PP#1F3974. The estimated dietary intake of seed screenings for dairy cattle remains unchanged.

** The proposed tolerance for corn forage of 12 ppm has been expressed on a dry weight basis as 48 ppm.

Table 5b

Worst Case Diet for Dairy Cattle

Commodity	Tolerance (ppm)	% Diet	Diet (ppm)
Grass, screenings	60	25	15
Corn Forage	48*	50	24
Corn Grain	0.1	25	0.03
		TOTAL	39

* Dry weight basis.

By using results from the 75 ppm dose level, required tolerances can be derived, as shown in the following table.

Table 6

Required Tolerances for Meat and Milk

Cattle Sample	Residue @ 75 ppm	Est. Residue from Diets	Required Tolerance (ppm)
Milk	0.08	0.04	0.05
Kidney	4.7	2.0	2.0
Liver	4.3	1.8	2.0
Fat	0.23	0.10	0.1
Meat	0.11	0.05	0.1

CBTS Comment

Ciba-Geigy's proposed tolerances are appropriate. We note that the tolerance on grass seed screenings is pending.

Anticipated residues will not be determined in this memo. A discussion appears in PP#1F3974.

Other Considerations

Ciba-Geigy has also submitted results from a market basket survey of grass seed screening pellets. The maximum residue of propiconazole is 15 ppm, which could be used in anticipated residue calculations. These results will be discussed in our review of PP#1F3974.

Tolerances on pineapples and pineapple fodder are appropriate (C. Deyrup, PP#8F3674, memo of 12/14/88).

cc: RF, Circu., PP#1F3974, Mike Flood, E. Haeberer, J. Fleuchaus (LE-132P).

H7509C:CBTS:Reviewer(MTF):CM#2:Rm804P:703-305-7990:typist(mtf):5/6/93.
RDI:SectionHead:ETHaeberer:5/4/93:BranchSeniorScientist:RALoranger: 5/5/93.

C. Reg File

Case No.:3125
Chemical No.:122101
CBRS No(s).: 9734, 9793, 9797
DPBarcode No(s).: D176899, D176958, D177496

CBRS TRANSMITTAL SHEET FOR PHASE 4 REVIEWS

Transmitted to HED on 4/30/92
Case name: Propiconazole
Chemical name(s): 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
Data submitter(s): CIBA-GEIGY Corporation

CRM: Bruce Sidwell/Richard Gebken (PM-53) Phone #: 308-8591

Issues/flags:

This action contains a request for a DATA WAIVER ( )
TIME EXTENSION ( )
ALTERED/DELETED USE ( )

Other: (i) Used information gathered from LUIS report (2/10/92) and product labels (EPA Reg. Nos. 100-617, 100-641, and 100-702). (ii) Under reregistration, TOX is expected to support the position that there is no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for the triazole moieties contributed by propiconazole based on existing toxicity data for triazolyl analine (per conversation between B. Cropp-Kohlligian of CBRS and E. Doyle of TOX 5/18/92). (iii) Data submitted concerning magnitude of the residue in/on mint (unregistered use site) and aquatic residue accumulation in rice and crayfish polyculture (pending action to remove crayfish aquaculture restriction) were not reviewed herein as they do not pertain to reregistration issues.

Case No.:3125
Chemical No.:122101
CBRS No(s).: 9734, 9793, 9797
DPBarcode No(s).: D176899, D176958, D177496

Branch: CBII, Reregistration Section II

Reviewed by: Bonnie Cropp-Kohlligian B. Cropp-Kohlligian Date: 6/25/92

Felecia A. Fort F. Fort Date: 6/25/92

Freshteh Toghrol, Ph.D F. Toghrol Date: 6/25/92

Approvals:

Section Head: William J. Hazel, Ph.D W. J. Hazel Date: 6/25/92

Branch Chief: Edward Zager Edward Zager Date: 6/25/92

Division Approval: Penelope Fenner-Crisp, Ph.D Penelope A. Fenner-Crisp Date: 6/30/92

cc: Ester Saito (HED), Part C Reregistration File, RF, SF, Circ., F. Fort, B. Kohlligian, F. Toghrol, C.Furlow (PIB, FOD), Betsy Grim (EFED).

Response, by Guideline

Guideline #: 171-4(a) Description: Nature of residue - plants
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
MRID Nos. 93194-062 Summary, 74500, 74501, 74502.

Discussion: The registrant submitted a summary of metabolism data concerning target (peanuts) and non-target crops (rotational crops such as corn, winter wheat, lettuce and carrots).

In one target crop study (ABR-80006 and ABR-80037), two groups of peanuts were grown in the greenhouse. One group was treated with triazole-^{14}C-propiconazole and the other with phenyl-^{14}C-propiconazole at a rate which totaled 0.92 lb ai/A. The plants were sprayed three times (at 5, 12, and 17 weeks of maturity) with an ethanol/water solution containing one of the radiolabeled propiconazole materials described above. Samples of stalks, kernels and shells were collected for analysis at 1- and 14-day PHIs. At maturity (14-day PHI), the phenyl- and triazole-^{14}C-propiconazole treated plants contained 4.4 and 2.9 ppm propiconazole equivalents in the stalks and 0.05 ppm and 0.33 ppm in the kernels, respectively, and 0.09 ppm in the shells for both radiolabelled positions. The activity of each plant part was characterized by extraction into organic and aqueous fractions (%TRR). Only peanut stalk samples collected at a 14-day PHI were further examined to identify metabolites. Less than 20% of the TRR in these samples was actually identified as propiconazole (13-15% TRR), CGA-91305 Alkanol (3-4% TRR), and OH-isomers B,C,C' (1% TRR and includes CGA-118244 and CGZ-118245).

In a second target crop study (ABR-81031), greenhouse grown peanuts were sprayed 8 times with triazole-^{14}C-propiconazole (formulation unspecified). The combined application rate was 0.8 lb ai/A. No further data were provided in the subject summary (MRID No. 93194-062).

In a non-target crop study (ABR-81013 and ABR-82007),

winter wheat, lettuce, corn, and carrots were grown in field plots in which peanuts had been previously grown and treated with triazole-^{14}C-propiconazole at 0.15-0.38 lb ai/A (EC formulation). The peanuts were harvested at a 16-day PHI and samples of stalks and kernels were collected and extracted into organic and aqueous fractions. Metabolites in peanut kernels were determined as Triazole Acetic Acid (3.8% TRR) and CGA-131013 Triazole Alanine (67.9% TRR). Residues were also characterized in rotational winter wheat, lettuce, corn, and carrot samples by extraction into organic and aqueous fractions. Fractions were further subjected to HPLC or TLC to separate individual metabolites. Metabolites identified in the non-target crop samples included Triazole Acetic Acid (2.4%-68.7% TRR), CGA-131012 Triazole Alanine (6.7%-79.4% TRR), polar metabolite I (4.9%-35.8% TRR) and polar metabolites E, F, G, H (1.0%-7.0% TRR). No parent compound was identified in any of the target or non-target crop samples. Identities of the metabolites were confirmed by mass spectroscopy or FTIR.

In a second non-target crop study (ABR-83030), one group of peanuts was grown in soil treated with triazole-^{14}C-propiconazole and another group was grown in soil treated with phenyl-^{14}C-propiconazole at 1.5 lb ai/A followed by rotational crops of winter wheat and corn. Peanuts were harvested at a 21.5-day PHI and samples of stalks, shells and kernels were collected and extracted into organic and aqueous fractions. Residues were also characterized in rotational winter wheat and corn by extraction into organic and aqueous fractions. Further characterization/identification was not provided in the subject summary (MRID No. 93194-062) for any of the target or non-target crop samples.

These metabolism studies are not adequate to satisfy plant metabolism data requirements. The summary of peanut metabolism data does not provide adequate characterization/identification of metabolites in peanut nutmeats (kernels) and hulls (shells) after treatment with triazole-^{14}C-propiconazole and there are no data demonstrating metabolite characterization/identification in peanut nutmeats or hulls after treatment with phenyl-^{14}C-propiconazole. Metabolism data from rotational studies (pre-planting applications) are not adequate to reflect registered uses which include foliar applications to wheat, barley and rye.

Note: Studies indicated as summarized in the title of

the subject summary (MRID Nos. 155644, 74496, 74499, 74497, 155646) were not consistent with studies which were actually included in the text of the subject summary (MRID Nos. 74496, 74498, 74497, 129915, 155645).

Brief review of other metabolism studies cited in the Registrant's Phase 2 response, but not reformatted or summarized by the registrant in support of reregistration in Phase 3, indicated the existence of data reflecting foliar treatments of triazole-^{14}C-propiconazole and phenyl-^{14}C-propiconazole to wheat (MRID Nos. 74500 and 74501) and grapevines (MRID No. 74502). Data, however, are limited in their utility to reflect typical use practices (a few plants grown in fields in Switzerland) and do not provide sufficient raw data concerning the phenyl-^{14}C-propiconazole treatment portions of the studies to determine the adequacy of the data.

No metabolism data were identified by the registrant reflecting uses of propiconazole radiolabelled in the dioxolan portion of the molecule.

Metabolism data provided concerning peanuts, grapes, lettuce, and carrots are of limited utility and are considered supplemental to required data since these crops do not represent registered use sites for propiconazole.

Data gap: The registrant must provide new plant metabolism studies. Phenyl-^{14}C-propiconazole should be applied to wheat, bananas, and pecans reflecting the currently registered use patterns. The specific activity and/or application rate should be high enough to allow for adequate identification of the metabolites/degradates. If metabolism is similar in these three unrelated crops then only these three must be tested.

The plant material from the metabolism studies should be tested using the data collection method(s) and enforcement analytical method(s).

Guideline #: 171-4(b) Description: Nature of residue - animals
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___

Discussion:

MRID No. 93194085. Summary of MRID Nos. 00074503 and Related MRIDs 00067905 and 00074504.

One lactating goat was fed triazole-^{14}C-propiconazole at a rate of 4.53 ppm for 10 days. The specific activity was 25.3 μCi/mg. Approximately 90% of the activity was excreted in the urine (69%) and feces (21%). The maximum residues found in milk, liver, kidney, fat, and muscle were 0.015 ppm, 0.96 ppm, 0.29 ppm, 0.008 ppm, and 0.01 ppm, respectively. Radioactivity plateaued in the milk by the third treatment day. No parent compound was found in milk or liver. Sulfate and glucuronide conjugates and components containing the triazole ring were found in milk. Characterization of the liver residues showed 80 to 90% of the activity was released by protease suggesting conjugation with amino acids. No ^{14}C was identified. The TOX Branch has concluded that the triazole ring is not toxicologically significant.

Interim tolerances exist (expiration date: 6/21/93) for residues of propiconazole in cattle, goat, hogs, horses, and sheep kidney and liver. In PP#9F3706 it was concluded that due to the possibility of significant dietary burden to cattle resulting from the use of propiconazole on grass that additional ruminant metabolism studies would be required before permanent tolerances could be established. MRID 41823301 and MRID 41823302 (review below) were submitted for that purpose.

MRID No. 41823301. No summary submitted.

Three lactating goats received phenyl-^{14}C-propiconazole for four consecutive days at a rate of 67 to 92 ppm in feed (10X to 14X the maximum dietary burden, MDB). 71.7 to 81.6% of the radioactivity was eliminated in urine and feces. The maximum residues found in milk, liver, kidney, fat, and muscle were 0.22 ppm, 3.83 ppm, 2.53 ppm, 0.09 ppm, and 0.08 ppm, respectively. 75 to 93% of the extractable activity (93 to 98% of the radioactivity was extractable) in tissue and milk was found in the organic phase extracts. Samples were analyzed by TLC, HPLC and/or GC/MS (HPLC/MS for milk samples). The percent characterized (identified in parentheses) was 66%(51%), 63%(32%), 69%(50%), 86% (86%), and 77%(52%) of the total ^{14}C in liver, kidney, muscle, fat and milk, respectively. Analysis of the organic extract of liver, kidney, muscle, and fat identified the parent, propiconazole (1.7-13.9% of TRR); 1-([2-(2,4-dichlorophenyl)-4-(2-hydroxypropyl)-1,3-dioxolan-2-

yl]methyl}-1H-1,2,4-triazole (CGA-188244)(9.4-34% of TRR); and 1-{[2-(2,4-dichlorophenyl)-2-hydroxy]ethyl}-1H-1,2,4-triazole (CGA-91305)(15.9-31.3% of TRR). An unknown component was also characterized but not identified (6.2-31.1%). CGA-188244(23%) and CGA-91305(24%) were identified in milk and four unknown components(35%) were also detected. Attempts to isolate and characterize the milk components by HPLC/MS were futile due to low levels of these components. The registrant suggested that they were aryl sulfate conjugates based on their chromatographic behavior after treatment with aryl sulfatase. The water extractable radioactivity from liver and kidney was characterized by TLC and the parent and CGA-188244 were found at low levels but not quantitated. 68 to 70% of the water extractable activity was found to be highly polar and was not identified. No attempt was made to characterize the unextractable activity (<5% of TRR).

MRID No. 41823302. No summary submitted.

No poultry metabolism studies have been previously submitted. Four laying hens were fed ^{14}C-phenyl labeled propiconazole for 8 consecutive days at a rate of 67 ppm in feed corresponding to 670X the maximum or expected dietary burden and were sacrificed six hours after the last dose. 73 to 87% of the radioactivity was eliminated in the excreta. 83% or more of the radioactivity was extractable with most activity (≥70%) extracted with acetonitrile (ACN). Identification of the components was accomplished using HPLC, GC/MS and TLC. The TRR level found in liver, kidney, fat, muscle, egg white, and egg yolk were 3.24 ppm, 3.33 ppm, 0.56 ppm, 0.32 ppm, 1.50 ppm, and 1.74 ppm respectively. The parent, propiconazole(1.4-39.0%), CGA-118244(1.5-50.0%), and CGA-91305(17.7-78.6%) were found in the organic extract (ACN) of tissue and eggs. The percentage of the TRR identified were 62%, 39%, 83%, 87%, 94%, and 75% in liver, kidney, fat, muscle, egg white, and egg yolk. Kidney ACN extracts were additionally treated with beta-glucuronidase and aryl sulfatase. The presence of conjugates was indicated after reaction with the aryl sulfatase. The remaining activity in the solids was not subjected to further analysis.

MRID No. 41823304. Method Validation.

Tissues (fat, liver, leg muscle), blood and milk from a goat and liver, breast muscle, and fat samples from a hen dosed with phenyl-^{14}C-propiconazole were

analyzed using Analytical Method AG-517. The extractability (i.e., % of TRR extractable) ranged form 82% to 103%. Recoveries of the TRR ranged from 70% to 111% with fortifications of 0.02 ppm to 5.0 ppm. Samples were analyzed in triplicate.

Data gap: Poultry metabolism data appears to be adequate for Phase 5 review. Additional identification of residues in the tissue and milk of the goat must be attempted including quantitative information concerning residues found in the water-extractable activity. Data must be provided that show the levels and identities of bound/conjugated residues present and, if applicable, proof of incorporation into natural constituents.

Guideline #: 171-4(c) Description: Res. analyt. method - plant
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
MRID Nos. 93194-066 and 93194-064 Summaries

Discussion: The registrant submitted a summary of the Ciba-Geigy analytical procedure, AG-454A, entitled, "Determination of Total Residues of Propiconazole in Crops as 2,4-Dichlorobenzoic Acid by Capillary Gas Chromatography". In brief, samples are extracted by refluxing with 20% concentrated ammonium hydroxide/methanol for one hour. The mixture is cooled and filtered. An aliquot of the extract is evaporated to dryness and the residue dissolved in NaOH. The sample is then heated for one hour and fifteen minutes with potassium permanganate, where propiconazole and its metabolites are converted to 2,4-dichlorobenzoic acid. Excess permanganate reagent is quenched with sodium metabisulfite and acid. After addition of water, the sample is partitioned with 10% diethyl ether/hexane. The organic phase containing the 2,4-dichlorobenzoic acid is evaporated to dryness and derivatized with diazomethane in the presence of dodecane which acts as a keeper to reduce losses, due to the volatility of the derivative, in subsequent steps. The derivative is cleaned up using an acidic alumina Sep-Pak®. The cleaned extract is analyzed by capillary gas chromatography with a DB-5 column and electron capture detection.

Fortification data were provided for various fractions of wheat, soybeans, corn, celery, peanuts, pecans, beans and peas fortified at 0.05-2.0 ppm of propiconazole.

Method AG-454A has undergone a successful method trial at the Analytical Chemistry Laboratory of the EPA using samples of wheat grain and pecan nutmeats fortified with propiconazole at 0.1 and 0.2 ppm and wheat straw fortified with propiconazole at 1.5 and 3 ppm. The method gave recoveries ranging from 79-107%. Method sensitivity was reported at 0.05 ppm for wheat grain and pecan nutmeats and at 0.2 ppm for wheat straw. Control samples contained residues less than the sensitivity of the method.

Method AG-454A has been deemed adequate for regulatory purposes and forwarded to FDA for editing and publishing in PAM II (memo S. Malak dated 5/28/87).

Propiconazole and its metabolites; Alkanol CGA-91305; β-hydroxy CGA-118244; and CGA-71019 (1,2,4-triazole) were subjected to the Multiresidue Method of analysis in PAM I, Protocols I, II, III, and IV. Test commodities included rice grain, rice straw, and pecan nutmeats. None of the test substances was detected by Protocol IV. With the exception of the triazole moiety, the remaining test compounds studied were detected by Protocols I, II, and III.

Analytical Method AG-454A uses diazomethane as a methylating agent to esterify the analyte. The registrant states that other methylating agents have been tried; however, they are deemed inferior in two respects: (i) they require more time for reasonable derivatization and (ii) they introduce interferences which would necessitate further cleanup before analysis. Diazomethane is, therefore, the reagent of choice.

Data gap: The registrant must submit data collection and regulatory analytical method(s) for the determination of propiconazole and its metabolites in/on banana commodities. If new metabolites (which require regulation) are found in the new plant metabolism studies, then analytical method(s) must be developed for them as well. Any regulatory methods submitted will require an independent method validation as described in PR Notice 88-5 (July 15, 1988). Propiconazole and its metabolites in banana must be tested through multi-residue Protocol(s) A, B, C, D,

and E.

If method validations of the multi-residue methods are found to be necessary, representative (including the most difficult) plant matrices must be tested.

The registrant must provide details concerning their efforts to find substitute methylating agents to replace the use of diazomethane in their regulatory enforcement method (AG-454A). The registrant should be aware that strong justification is needed for the use of diazomethane and adequate documentation must be provided supporting the need for the use of this hazardous reagent.

Guideline #: 171-4(d) Description: Res. anal. method - animals
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: Y
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: **MRID 93194067. Summary of 40180702 and 40145401.**

Analytical Method AG-517. Animal tissues are extracted with 20% water/acetonitrile (milk and eggs are extracted with acetonitrile), filtered and evaporated to dryness. The resulting residue is dissolved in NaOH and heated with potassium permanganate to convert to 2,4-dichlorobenzoic acid (DCBA). After partitioning with 10% diethyl ether/hexane, the organic phase is evaporated to dryness and derivitized with diazomethane to the methyl ester followed by a clean up using acidic alumina. The extract is analyzed by GC/ECD. The LOQ is 0.05 ppm for meat and egg and 0.02 for milk expressed as propiconazole equivalents. The recoveries ranged from 70-135 (96% avg.), 82-127 (105% avg), 64-128 (89% avg), 77-90 (84% avg), 63-87 (75% avg) for liver, round tissue, fat, eggs, and milk, respectively. A successful method trial has been performed.

MRID 93194060. Summary of MRID 40100101.

Propiconazole, CGA-91305, CGA-118244, and CGA-71019 were subjected to Multiresidue Methods of Analysis of PAM I, Protocols I, II, III, and IV. All four compounds were amenable to Protocol I, GC analysis. None of the test compounds were detectable in Protocol IV. With the exception of CGA-71019, the remaining

test compounds were detected by Protocols I, II, and III.

Data gap: Analytical Method AG-517 appears to be adequate for enforcement and data collection involving propiconazole residues containing the 2,4-dichlorobenzene ring in animal tissues, eggs and milk. This method is acceptable for Phase 5 review. The registrant must demonstrate attempts to use alternative methylating agents if this method is proposed as a livestock regulatory method due to the dangerous and toxic nature of diazomethane. [Additional methodology may be required if new residues of concern are discovered in the required livestock metabolism studies.]

Guideline #: 171-4(e) Description: Storage stability
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: **MRID 93194068. Summary of MRID 00133385 and Related MRIDs 00074510 and 00074511.**

Fortified samples of control soybean fodder and grain (0.4 ppm propiconazole) and field weathered samples of peanut fodder, shells, and nutmeat were stored in glass jars at -15 C for 6 months and 37 months, respectively. No 0 day analysis was conducted on peanuts (samples were stored frozen in October, 1980 and initially analyzed in September, 1981). Samples were analyzed again in October, 1983. Analytical method AG-354 was used to determine residues in soybean. Recoveries of parent, propiconazole averaged 94 to 98% for fortifications of 0.40 ppm. Analytical method AG-356 was used to ascertain residues determined as 2,4-dichlorobenzoic acid methyl ester and converted to propiconazole equivalents in peanuts. Recoveries of fortifications of 0.05 to 10.0 ppm of propiconazole averaged 92 to 108%. Residues were found to be stable for up to six months (91% recovery) in soybean fodder and for up to four months (75% recovery) in soybean grain. In the case of peanuts, after 25 months (period between initial and final analysis), 95 to 333% of the initial residues were found. Residues were found in the control samples

(0.15 and 0.23 in peanut fodder and shells, respectively) and declined by 60 and 48% after 25 months. No studies were conducted on animal commodities.

Data gap: Data presented for residues of propiconazole in or on soybean fodder and grain are sufficient to show that residues are stable in soybeans for 4 to 6 months; however most studies submitted to satisfy requirements of reregistration were stored for periods longer than six months (up to 35 months). Storage stability data for peanut fodder, shells and nutmeat are completely inadequate. No initial analysis was performed, control samples showed high residues, and recoveries were extremely excessive bringing in to doubt the integrity of the study. In addition peanut and soybeans are not registered use sites and storage stability data generated on these legumes can not be translated to registered crops since they are unrelated (no legume tolerances). Storage stability studies must be conducted on all crops and processed products for which a field trial and/or processing study has been (or will be) conducted, as well as representative livestock commodities. Use of field-weathered samples is strongly recommended. Storage conditions must reflect the storage conditions of the treated samples (from the field trial and processing studies) with respect to temperature, length of storage, containers, lighting, etc. If there are any metabolites and/or degradates included in the tolerance expressions, then they must be tested as well. The chosen intervals must allow for unforeseen delays in sample storage.

Guideline #: 171-4(f) Description: Mag. res. - potable water
Is requirement applicable? (Y/N): N

This is N/A because there are current label restrictions which prohibit the use of propiconazole on rice in CA (where typical agricultural practices for rice field irrigation entails a "flow-through" system) and because typical agricultural practices concerning rice field irrigation in all other areas allows for the on-site evaporation of waters used in rice fields.

Guideline #: 171-4(g) Description: Magnitude residue - fish
Is requirement applicable? (Y/N): N

This is N/A because label restrictions preclude use where catfish and crayfish are produced.

Guideline #: 171-4(h) Description: Mag. res. - irrigated crop
Is requirement applicable? (Y/N): N

This is N/A because label restrictions preclude the use of water drained from treated rice fields to irrigate other crops.

Guideline #: 171-4(i) Description: Mag. res. - food handling
Is requirement applicable? (Y/N): N

Guideline #: 171-4(j) Description: Mag. meat/milk/poultry/eggs
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: Tolerances have been established for propiconazole residues in fat, meat, and meat by-products (except kidney and liver) of all livestock. Interim tolerances exist (expiration date: 6/21/93) for residues of propiconazole in cattle, goat, hog, horse, and sheep kidney and liver. In PP#9F3706 is was concluded, that due to the possibility of significant dietary burden to cattle resulting from the use of propiconazole on grass, additional ruminant metabolism studies would be required before permanent tolerances could be established.

MRID No. 93194070 Summary of MRID No. 00137861.

Four dose groups of dairy cows were fed propiconazole at rates of 0, 15, 75, or 150 ppm in the diet. These rates correspond to 2.3X, 11.5X, and 23X the maximum dietary burden (MDB). Three cows were fed at each dose

level. One cow from each group was sacrificed at 14, 21, and 28 days. All animals were sacrificed within 7 hours of receiving their last dose. The analytical method used was AG-354, a GC-FID method, for determination of parent compound and AG-359 (GC-ECD) for determination of the total residues determined as 2,4 dichlorobenzoic acid methyl ester. No validation data relative to animal tissues and milk were submitted for this method. Residues in milk plateaued on or before day 14 at the two higher dose rates. Residues ranged from ND(<0.05 ppm) in fat, blood, and muscle to 0.81 in liver at the 15 ppm feeding level (2.3X MDB). No detectable residues (<0.01 ppm) were found in milk at the 15 ppm feeding level. Samples were stored at -15°C for 1 to 2 months. No storage stability data were provided.

Four dose groups of laying hens were fed propiconazole at rates of 0, 7.5, 37.5 or 75 ppm corresponding to a maximum dietary burden (MDB) of 75X, 375X, and 750X. Each dose group contained fifteen hens. Three chickens from each of the four treatment groups were sacrificed on days 7, 14, 21, and 28 of the test. Residues plateaued in eggs between 14 and 21 days at the two higher dose rates. The analytical method employed was AG-354, a GC-FID method, for determination of parent compound and AG-359 (GC-ECD) for determination of the total residues determined as 2,4 dichlorobenzoic acid methyl ester. No validation data were provided to establish the validity of the method as it pertains to poultry tissue and eggs. No detectable residues (<0.10 in liver and <0.05 in muscle, fat, skin and eggs) were found at the 7.5 ppm dose rate (75X MDB). Samples were stored at -15C for 3 to 4 months. No storage stability data were provided.

Data gap: Acceptance of the feeding studies is contingent upon submission of adequate validation of the methods used for analysis (AG-354 and AG-359) and adequate storage stability studies for livestock commodities. If additional metabolites of concern are found in metabolism studies, then additional magnitude of residue data will be required.

Guideline #: 171-4(k) Description: Banana
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N

Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: **MRID 93194071. Summary of MRID 00137150.**

Propiconazole is currently not registered for use on bananas in the United States. An import tolerance exists at 0.20 ppm. No translated label was submitted for review. One to thirteen aerial or ground applications of TILT 250EC in water or oil at a rate of 100g ai/hectare/application were applied foliarly to bananas in Honduras, Republic of Ivory Coast, Martinique, and Belize. Spray intervals ranged from 10 to 42 days. Other field trials were conducted at a rate of 200 g ai/ha/application with seven to eight ground applications in water or oil using the same formulation. Analyses were conducted using Analytical method REM 11/81 for determination of the parent and AG-356 for determination of total residues. Validation of REM 11/81 using banana peel and pulp samples fortified with 0.04 to 0.40 ppm of propiconazole resulted in recoveries ranging from 63 to 151% (95% avg). Recoveries using AG-356, determined as the methyl ester, and fortified with 0.1 to 1.0 ppm propiconazole produced recoveries of 61 to 137% (avg. 98%). PHI's ranged from 0 to 21 days. With the exception of one sample(7 appl. at 200 g ai/ha/app) resulting in total residues of 0.21 ppm, all residues were less that 0.20 ppm. No storage stability studies were performed for bananas. Samples were stored up to 11 months at -15 C prior to analysis.

Data gap: The adequacy of these field trials will not be assessed until representative translated labels for this use in major banana-producing countries are submitted. Adequate storage stability data must be submitted.

Guideline #: 171-4(k) Description: Grasses Grown for Seed
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N/A
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: **MRID 93194073 Summary of MRID 40890701.**

Five field trials were conducted in Oregon, and Minnesota using bluegrass, fescue, and ryegrass. Three to four ground applications of Tilt 3.6E

formulation were applied at a rate of 50, 100 or 200 g ai/A/app. at 14 to 21 day intervals. The maximum amount applied was 400 g ai/A/season with the exception of one trial conducted at the 2X level (800 g ai/A/season maximum). PHI's ranged from 20 to 36 days in hay and seed, and 141 to 149 days in forage. The maximum residues found were 1.3 ppm, 2.1 ppm, and 0.24 ppm in hay, seed, and forage in bluegrass; 1.4 ppm and 1.3 ppm in hay and seed in fescue; and 3.3 ppm, 3.5 ppm, and 0.12 ppm in hay, seed and forage in ryegrass determined as 2,4 dichlorobenzoic acid methyl ester using analytical method AG-415. Recoveries using this method from grass hay and seed samples fortified with 0.1 to 2.0 ppm of propiconazole ranged from 72 to 111% (avg. 88.4 %). Control samples of hay, seed, and forage ranged from <0.05 to 0.18 ppm total residues. One control sample of ryegrass chaff showed residues of 0.51 ppm. Samples were stored at -15°C for up to 5 months before analysis.

Data gap: Interim tolerances are established for this use on grasses grown for seed and these will expire on June 21, 1993. A petition for permanent tolerances has been submitted and found to be insufficient (see S. Willett, 6/11/91). Deficiencies cited were (i) lack of information about storage, (ii) trials not reflecting label directions, and (iii) high residues in control samples. CBRS will not address this use as it pertains to registration.

Guideline #: 171-4(k) Description: Pecans
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
Discussion: **MRID 93194074 Summary of MRID 74508, 74509, 74495, and 153327.**

6 to 10 foliar applications of CGA-64250 3.6E (Orbit) at a rate of 150 g a.i./A/appl. beginning at bud break with two-week intervals between applications until shuck-split were applied by ground application in eight studies. Field trials were conducted in Alabama, Georgia, Louisiana, Mississippi, New Mexico, Oklahoma, and Texas, accounting for 93% of the pecan production. The general directions for use in all areas are as follows: Apply 4 fl. oz. (51 g.a.i./A)

at bud break repeating at two week intervals, not to exceed 4 applications. For treatment of pecan scab in the South, 4 fl. oz. at 14-day intervals during bud break and 8 fl. oz. during nut formation and cover sprays is directed. In the Southwest for treatment of pecan scab, 4 fl. oz. at 14 day intervals during bud break and 6 fl. oz. in case bearer and cover sprays is recommended. In all areas, do not apply after shuck-split. No PHI is established. All field trials were conducted using ground applications, although aerial applications are permitted. Treatments in the field trials correspond to 2X or greater the label rate. Analysis was performed using Analytical Method AG-356, AG-359, AG-454. Recoveries using method AG-356 from pecan nutmeat samples fortified with 0.05 to 2.0 ppm of propiconazole ranged from 56 to 67% and was used for studies conducted in Alabama, Oklahoma and Georgia. Recoveries using method AG-359, corresponding to studies conducted in Louisiana, Texas, and New Mexico, ranged from 31 to 89% (61% avg). Recoveries using method AG-454 ranged from 88 to 112% (102.3% avg.) and was used in studies conducted in Alabama and Mississippi. No detectable residues were found (<0.10 ppm, <0.05 ppm) in any of the samples.

Data gap: Although no detectable residues were present at exaggerated rates, the analytical methods used in >90% of the studies are not adequate due to low recoveries. New field trials must be conducted at the maximum rate schedules for the South and Southwest in Georgia and Texas, respectively, using the 3.6EC formulation at 14-day intervals beginning at bud break. Although not required, one or two studies reflecting exaggerated rates will assist CBRS in determining the validity of previous studies submitted. In addition, an amendment must be proposed to add a PHI and a maximum number and/or seasonal maximum rate to the 3.6 EC label.

Guideline #: 171-4(K/1) Description: Rice field trials/process
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
MRID Nos. 93194-075 and 93194-079 summaries.

Discussion: Six rice studies representing three growing seasons

were conducted in AR (2), LA (1), MS(1), and TX (2 in same location/growing season). Two treatments with a 3.6 EC formulation of propiconazole were made at 75 g ai/A at internode elongation and again at boot stage or one treatment was made at 125 g ai/A at first internode elongation by ground (20-25 GPA) or aerial (10 GPA) application methods. Residues in/on rice grain ranged from <0.05 to 0.07 ppm and in/on rice straw from 0.05 to 2.08 ppm at 46- to 80-day PHIs. Field trials were conducted at exaggerated rates (1.67-3.34x) using one to two applications of 125-250 g ai/A of propiconazole. The timings of the applications were not specified. Residues in/on grain samples depicted in the exaggerated study were <0.05 ppm at 53- to 67-day PHIs. Only one rice straw sample contained detectable residues (0.09 ppm) resulting from a single application at 250 g ai/A.

Rice grain and straw samples were stored at -15°C for 0-27 months prior to analysis. No concurrent storage stability data were provided. Analyses were conducted using either method AG-415 or AG-454A in which residues are determined as 2,4-dichlorobenzoic acid methyl ester and expressed as propiconazole equivalents. Recoveries from rice and processed rice fraction samples fortified with 0.05 to 0.50 ppm of propiconazole and analyzed concurrently with the field-treated samples using method AG-415 were 64-152% and using method AG-454A recoveries of rice grain samples fortified at 0.05 to 1.00 ppm were 75-110%.

Rice residue data may not be adequate to support the established tolerances on rice grain (0.1 ppm) and straw (3.0 ppm) since the minimum possible PHI [reviewer estimated minimum PHI at <49-days based on minimum possible time between panicle differentiation (closely associated with internode elongation stage) and maturity] is not specified on the label and may not be adequately represented by the available data base.

The registrant also provided rice processing data from three field studies conducted in AR which included two old studies and one new study. Tests conducted which reflected maximum use rates of propiconazole (1x) made at internode elongation only (125 g ai/A) or at internode elongation (75 g ai/A) followed by a second application at boot stage (75 g ai/A) resulted in nondetectable residues (<0.05 ppm) in/on rice grain samples at 53- to 67-day PHIs. In other tests conducted using higher use rates (1.3x-3.4x) and/or later applications (heading stage), residues of

propiconazole in rice grain samples ranged from <0.05 to 2.2 ppm at 20- to 67-day PHIs. Rice grain samples were processed into hulls, unpolished brown rice, polished white rice, and rice bran on a small scale in a laboratory by procedures that were intended to simulate industrial practices.

One of the two studies (7784; SW-FR-103-803) previously submitted provided residues of propiconazole in the rice grain samples which were <0.05 ppm even when exaggerated rates were used (up to 3.3x). This study is, therefore, limited in its utility to determine the potential for concentration of residues in rice processed commodities.

The other study (6230; SW-FR-104-80) which was previously submitted was conducted using exaggerated use rates and conditions (applied at heading) and showed detectable residues in the rice grain samples and a concentration in the hulls (1.5-3.3x) only. [Note: Summary report (MRID No. 93194-079) erroneously reported the total propiconazole residues in one grain sample (Desha, AR; 6230; SW-FR-104-80; 3.4x application) as 2.2 ppm when the original report (MRID No. 74508 pg. 28) reported a value of 1.5 ppm.]

The third processing study had not been previously submitted according to the registrant's summary and was conducted using exaggerated rates (1.3-3x) at the normal application periods (internode elongation and again at boot stage) producing some detectable residues in/on rice grain samples (<0.05-0.14 ppm) and a concentration of residues in hulls (2.1-3.6x) and bran (1.7-3.6x).

Total residues of propiconazole and its metabolites containing the 2,4-dichlorobenzyl moiety were determined by methods AG-356, AG-415, and AG-454A. Recoveries of propiconazole, determined as 2,4-dichlorobenzoic acid methyl ester and converted to propiconazole equivalents from rice grain and processed rice products were 92-106% for AG-356 when fortified with 0.05 to 2.0 ppm of propiconazole, 69-152% for AG-415 when fortified with 0.05 to 0.20 ppm of propiconazole, 90-127% for AG-454A when fortified with 0.05 to 1.0 ppm of propiconazole. Rice grain and rice processed fractions from the processing studies were stored at -15°C for 0-35 months prior to analyses. No concurrent storage stability data concerning processed products were provided.

Current registrations of propiconazole to rice include

the following restrictions: (i) Do not apply to stubble or ratoon crop rice; (ii) Do not use in rice fields where commercial farming of crayfish will be practiced; (iii) Do not drain water from treated rice fields into ponds used for commercial catfish farming; (iv) Do not use water drained from treated fields to irrigate other crops; and (v) Do not use in CA.

Data gap: The registrant must amend all pertinent propiconazole product labels to include a minimum PHI (days) for use on rice reflecting available field trial data. Otherwise, rice field trials depicting residues of propiconazole and the regulated metabolites in/on rice will be required. If data generation is the chosen option, the EC formulation must be applied at the maximum label rate, the maximum number of applications, and the minimum PHI [as specified on the amended propiconazole labels]. Tests must be conducted in AR, LA, TX, and MO which represent ca. 70% of the major rice production regions according to the 1990 Edition of Agricultural Statistics.

Since detectable residues have been found on rice grain as a result of the maximum allowable use rate, grain dust data are required. Also, the newly submitted rice processing study (8593; SW-FR-103-84) conducted in AR which used exaggerated application rates and typical application timings produced (in some cases) residues in/on rice grain samples and a concentration of residues in processed rice hulls (3.6x) and bran (3.6x). Therefore, the registrant must propose FATs for residues of propiconazole and its regulated metabolites in/on processed rice hulls and bran at 3.6x the established (or amended, if applicable) RAC tolerance.

Guideline #: 171-4(k/l) Description: Wheat, barley, and rye field trials/process
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
MRID Nos. 93194-072 and 93194-080 summaries.

Discussion: Ten wheat studies representing three growing seasons were conducted in OH (1), NY (1), IL (1), NC (1), MS (3 in same location), and KS (3 in same location). One to two treatments with a 3.6 EC formulation of propiconazole were made at 50-100 g ai/A (1-2x) by

ground (5-50 GPA) or aerial (5 GPA) application methods at Feekes growth stage 8 (emerging flag leaf) or earlier. Residues in/on wheat grain ranged from <0.05 to 0.08 ppm at 42- to 80-day PHIs. Residues in/on wheat straw ranged from 0.08 to 4.7 ppm at 47- to 80-day PHIs.

Barley studies representing two growing seasons were conducted in North Dakota (1), Nebraska (1), and California (2 in same location). One treatment with a 3.6 EC formulation of propiconazole was made at 50 g ai/A (1x) by ground (10-30 GPA) application methods. Residues in/on barley grain were <0.05 ppm and in/on barley straw were from 0.07 to 1.0 ppm at 39- to 69-day PHIs.

Wheat grain and straw samples were stored at -15°C for 3-33 months prior to analysis. No concurrent storage stability data were provided. Analyses were conducted using either method AG-415 or AG-454 (which the registrant claims to be equivalent to the reformatted AG-454A) in which residues are determined as 2,4-dichlorobenzoic acid methyl ester and expressed as propiconazole equivalents. Recoveries from wheat and barley straw and grain samples fortified with 0.05 to 0.50 ppm of propiconazole and analyzed concurrently with the field-treated samples using method AG-415 were 47-168% and using method AG-454 were 69-124%.

No field studies were provided for rye. Adequate wheat and barley field studies could be translated to rye.

Wheat and barley residue data may not be adequate to support the established tolerances on wheat, barley, and rye grain (0.1 ppm) and straw (1.5 ppm) since the minimum possible PHI [reviewer estimated minimum PHI at 47-days based on application to spring wheat at Feekes growth stage 8 (42-days after planting) and a minimum growth period of 90-days] is not specified on the label and may not be adequately represented by the available data base (only one wheat and two barley field trials were conducted at ≤47-day PHIs) and because the submitted field studies are not sufficient to reflect all of the principle growing regions of wheat (21% geographical representation), barley (28% geographical representation) and rye (no tests) as indicated in the 1990 Edition of Agricultural Statistics.

The registrant also provided wheat processing data from two field trials conducted in KS and MN. Ground

applications of propiconazole were made at 1x to 3x in the KS field trials at 43- to 62-day PHIs and at 4x to 8x in the MN field trials at a 29-day PHI. Propiconazole residues in/on the wheat grain samples were <0.05 ppm and 0.15-0.29 ppm in the KS and MN tests, respectively. Wheat grain samples were processed into germ, shorts, bran, red dog, and flour on a small scale in a laboratory by procedures that were intended to simulate industrial practices. Propiconazole residues in processed wheat germ, shorts, red dog, and flour did not indicate any concentration of residues. Detectable propiconazole residues in/on wheat grain samples collected in the MN study (0.15-0.29 ppm) concentrated up to 5x in processed bran samples (0.54-1.40 ppm).

Residues of propiconazole and its metabolites containing the 2,4-dichlorobenzyl moiety were determined by methods AG-407, AG-415, and AG-344/AG-359. Recoveries of propiconazole, determined as 2,4-dichlorobenzoic acid methyl ester and converted to propiconazole equivalents from wheat grain and processed wheat products fortified with 0.05 to 0.50 ppm of propiconazole were 61-128% for AG-407, 60-132% for AG-415, 60-92% for AG-359. Wheat grain and wheat processed fractions from the processing study were stored at -15°C for <1-13 months prior to analyses. No concurrent storage stability data concerning processed products were provided.

Data gap: The registrant must amend all pertinent propiconazole product labels to include a minimum PHI (days) for use on wheat, barley and rye reflecting available and/or new field trial data. Field trial data depicting residues of propiconazole and any regulated metabolites in/on wheat are required. The EC formulation must be applied at the maximum label rate, the maximum number of applications, and the minimum PHI [as specified on the amended propiconazole labels]. Two tests must be conducted in separate parts of ND, WA, and OK which represent major wheat production regions according to the 1990 Edition Of Agricultural Statistics.

The wheat processing study conducted in MN which used exaggerated application rates and treatments at abnormal growth stages resulted in residues in/on grain samples and a concentration of residues in processed wheat bran (5x). Therefore, the registrant must propose FATs for residues of propiconazole and its regulated metabolites in/on processed wheat and

barley bran and rye feed at 5x the established RAC tolerances. Otherwise, the registrant must provide new wheat data using exaggerated rates equivalent to at least the theoretical concentration factor at the normal application period (Feekes growth stage 8). If no detectable residues are found on the RAC in these studies, then processing data/FATs are not required.

Since detectable residues have been found on some wheat grain samples as a result of the maximum allowable use rate, grain dust data are required.

Guideline #: 171-4(k/l) Description: Sugarcane Seed Piece field trials/process
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: N
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___
MRID No. 93194-077 Summary.

Discussion: The registrant supplied a study in which sugarcane seed pieces were dipped in a solution of triazole-^{14}C-propiconazole at concentrations of 1x (27 ppm), 2x (57.2 ppm), 5x (129 ppm), 10x (258 ppm), and 20x (515) prior to planting in test fields in HI. Only plants grown from the sugarcane seed pieces treated at 1x and 2x rates were sampled at 4, 8, 12, 16, and 58 weeks after germination. The 5x, 10x and 20x portions of the study were dropped after 6-months due to phytotoxicity. Residues were analyzed by combustion of plant parts followed by the determination of $^{14}CO_2$ by LSC. No radioactive residues (<0.01) were found in any plant part after 6 months for any of the application rates. Only one sugarcane sample (taken in duplicate) from the 2x study at a 58-week PHI was collected, analyzed, and processed into bagasse, raw sugar, and molasses. No radioactive residues (<0.01 ppm) were found in the RAC or processed commodities.

This study is limited in its ability to represent the major growing regions of sugarcane which include FL and HI and while the Section 3 registration only allows for the use of propiconazole on sugarcane seed pieces in HI, there is a 24(c) SLN registration for a similar use in FL. Also the study is inadequate because the test substance used was radiolabeled in the triazole ring portion of the molecule only. Data may not, therefore, reflect total toxic residues since

the current residues of concern are the parent and its metabolites determined as 2,4-dichlorobenzoic acid.

Data gap: Magnitude of the residue data must be generated using phenyl-^{14}C-propiconazole radiolabelled test material on sugarcane conducted in FL (assuming that the registrant wishes to support the 24(c) SLN registration FL88001600) and HI must be generated. If no residues (activity) are detected in the aerial portions of the growing crop at normal PHIs, then the treatment can be considered a non-food use. Otherwise, the treatment will be considered a food use requiring tolerances and conventional field trials in support thereof.

Guideline #: 171-4(k/l) Description: Corn Seed Piece field trials/process
Is requirement applicable? (Y/N): Y
Does the summary/available information indicate that the MRID is a candidate for Phase 5 review?: ___
Data Waiver( ) Time Extension( ) Other ( )
Data Waiver/Time Extension (If applicable) Granted? (Y/N): ___

Discussion: There are current 24(c) SLN registrations (HI88000300 and TX88000100) for use of propiconazole on field corn grown for seed according to the LUIS report (02/10/92). However, the registrant did not provide any response concerning this use in Phase 2 or 3.

In order to support these 24(c) SLN registrations for the use of propiconazole on corn, in the absence of any established tolerance in/on corn commodities, the use must be considered a non-food use.

Data gap: In the absence of established tolerances of propiconazole residues in/on corn commodities, the registrant must provide cultural practice information which outlines the rationale as to why currently active 24(c) SLN registrations (HI88000300 and TX88000100) for use of propiconazole on corn grown for seed only should be considered non-food uses along with the individual State's assurances that these seed crops will not be diverted to food or feed items. Otherwise, all such active 24(c) SLN registrations (HI88000300 and TX88000100) should be cancelled until such time as the registrant may propose and adequately support the establishment of tolerances in/on corn commodities resulting from the proposed uses.

ADDITIONAL COMMENTS:
The registrant is advised to consult the Subdivision O Residue Chemistry Guidelines, the Standard Evaluation Procedures, the Data Reporting Guidelines, and the Phase 3 Technical Guidance concerning the conduct of residue chemistry studies. If the registrant has additional concerns they are advised to submit a protocol for CBRS review.

PRODUCT CHEMISTRY

Case No.: 3125 Case Name: Propiconazole (List C Chemical).
Chemical No(s).: 122101 (CBRS # 9734; DP BARCODE: D176958)
Chemical Name(s): 1[[2-(2,4 dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
Registrant: CIBA-Geigy Corporation

Guideline Number	Is requirement applicable?	Does summary or available information indicate MRID is a candidate for Phase 5 review?	Are additional data required?	MRID Number
61-1	Y	Y	N	93194-001
61-2(a)	Y	N	Y[1]	93194-001
61-2(b)	Y	Y	N	93194-001
62-1	Y	Y	N	93194-002
62-2	Y	Y	N	93194-002
62-3	Y	Y	N	93194-002
63-2	Y	N	Y[2]	420302-01
63-3	Y	N	Y[2]	420302-01
63-4	Y	N	Y[2]	420302-01
63-5	N	N/A	N[3]	
63-6	Y	N	Y[2]	420302-01
63-7	Y	N	Y[2]	420302-01
63-8	Y	Y	N	420302-01
63-9	Y	Y	N	420302-01
63-10	Y	N	Y[2]	420302-01
63-11	Y	N	Y[2]	93194-005
63-12	Y	N	Y[2]	420302-01
63-13	Y	N	Y[2,4]	93194-005

Key: Y=yes; N=no; S=fully satisfies requirement;
N/A=not applicable.

1. These data do not satisfy the requirements of 40 CFR §158.160 and §158.162 (Guidelines Reference No. 61-2(a) regarding starting materials and the manufacturing process for the propiconazole technical because the following were not provided: (i) the name and address of the manufacturer/producer of the starting materials; (ii) the duration of each step of the process and of

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON DC 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

FEB 1 1989

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TILT Fungicide - Use on Grass Grown For Seed
Amendment to Pesticide Petition 9F3706

TO: Mr. Larry Schnaubelt, Acting Product Manager 21
Registration Division (TS-767)

FROM: Byron T. Backus, Toxicologist Byron T. Backus 1-25-89
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (TS-769C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 1/26/89
Acting Section Head, Review Section II
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (TS-769C)

and

Marcia van Gemert, Acting Branch Chief Marcia van Gemert 1/26/89
Fungicide/Herbicide/Antimicrobial Toxicology Branch
HED (TS-769C)

EPA Record No. 237877

Project No. 9-0659A

EPA Reg. No. 100-617

Tox. Chem. 323EE

Background:

The registrant (Ciba-Geigy Corporation) is proposing establishment of a tolerance of 10.0 ppm for propiconazole and its metabolites determined as 2,4-dichlorobenzoic acid and expressed as the parent compound in or on grass screenings used as livestock feed.

Comments and Recommendations:

1. The memorandum of December 16, 1988 from Linda S. Propst, Dietary Exposure Branch, states in part that tolerances established for residues of Propiconazole in or on the fat and meat of cattle as well as milk would appear to cover tolerances in these commodities from feeding livestock grass with 20 ppm residue, but secondary residues in kidney and liver might exceed established tolerances of 0.2 ppm.

2. Ciba-Geigy is proposing establishment of a tolerance of 10 ppm for Propicanazole and its metabolites in or on grass screenings used as livestock feed. Part of the supporting data for this tolerance is from a 3-level dairy feeding study in which residues were found in kidney and livers (but not milk, omental fat, perirenal fat, tenderloin or round) of cattle which were fed 15 ppm.

3. HFASB would have no objections, based on toxicological considerations, to the feeding of treated hay and grass seed screenings with a residue of 10 ppm Propiconazole to livestock, provided that the resulting secondary residues are within the limits of established tolerances, which are indicated below:

milk	0.05 ppm
kidney, liver	0.2 ppm
omental fat, perirenal fat, tenderloin, round	0.1 ppm

4. HFASB defers to the Dietary Exposure Branch as to whether or not the established tolerances indicated above will be exceeded.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response to DEB's Recommendation (Memorandum of 2/15/89) Regarding Tolerances with Expiration Dates for Tilt[R]

FROM: Byron T. Backus, Toxicologist Byron T. Backus 2/23/89
Herbicide/Fungicide/Antimicrobial Support Branch
HED (TS-769C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 2/23/89
Acting Section Head, Review Section II
Herbicide/Fungicide/Antimicrobial Support Branch
HED (TS-769C)

and K. Clark Swentzel for 2/23/89

Marcia van Gemert, Acting Branch Chief
Herbicide/Fungicide/Antimicrobial Support Branch
HED (TS-769C)

TO: Richard D. Schmitt, Ph.D., Acting Chief
Dietary Exposure Branch
HED (TS-769C)

and

Mr. Larry Schnaubelt, Acting Product Manager 21
Fungicide-Herbicide Branch
Registration Division (TS-767)

EPA Reg. No. 100-617

Tox. Chem. 323EE

Background:

The Dietary Exposure Branch has responded to a memorandum from HFASB (2/1/89) on adequacy of established tolerances for residues of Propiconazole in/on livestock commodities as a result of the feeding of treated grass screenings to livestock. DEB has stated that, in a worst case scenario, residues containing the chlorophenyl moiety may exceed established tolerances of 0.2 ppm for liver and kidney, reaching 1.5-2.0 ppm.

Comments and Recommendations:

1. HFASB concurs with DEB that a major concern in the issuance of these tolerances involves the inadequacy of the characterization of only approximately 21% of the residues of potential toxicological significance (particularly as the parent compound and some of the metabolites contain the chlorophenyl moiety) in the previously submitted livestock metabolism study.

2. HFASB would not object to establishment of tolerances with expiration dates on the subject feeds with concomitant revised tolerances of 2.0 ppm (with expiration date) for liver and kidney, provided Ciba Geigy is committed to generating data to address the deficiencies indicated in the DEB memorandum of 2/7/89 (H. Fonouni to L. Rossi).

End of Document

11520 N. Bradley

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

180.434

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MAY 28 1987

6/2/87 MJK

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Ms. Alice Marcotte
Technical Editing Group HFF-40
Food and Drug Administration
200 C Street, S. W.
Washington, D. C. 20204

Dear Ms. Marcotte:

Enclosed please find a copy of Ciba-Geigy's Analytical Methods AG-454A and AG-517 for their fungicide, propiconazole (Tilt®, Banner®, or CGA-64250). Permanent tolerances have been established for residues of propiconazole, 1-[[2(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl] methyl]1H-1,2,4,-triazole, in/on the grain of wheat, barley, rye, and rice at 0.1 ppm; straw of wheat, barley, and rye at 1.5 ppm; rice straw at 3 ppm; eggs at 0.1 ppm; milk at 0.05 ppm; meat, fat, and meat by-products (except liver and kidney) of cattle, goats, hogs, horses, poultry, and sheep at 0.1 ppm; and in the kidney and liver of cattle, goats, hogs, horses, sheep, and poultry at 0.2 ppm (PP#4F3074); pecan nutmeats at 0.1 ppm (PP#4F3007); and bananas at 0.2 ppm (PP#4E3026). The chemical is regulated under 40CFR§180.434.

Methods AG-454 has been successfully tried on wheat grain, pecan nutmeat, and wheat straw. Method AG-517 has been successfully tried on beef liver, whole milk, and eggs.

If you have any question about the enclosed material and I can be of any assistance, please let me know.

Sincerely,

Sami Malak

Sami Malak, Ph.D., Chemist
US EPA/OPP (TS-769C)
401 M St, S. W.
Washington, D. C. 20460
(703)557-4379

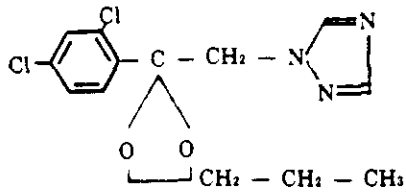
Attachment 1

PAM II Cover Sheet Page 1 of 1

Acceptable Name: propiconazole, 1-[[2-(2,4-dichlorophenyl) -4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1, 2,4-triazole.

Pesticide Reg. Section: §180.434

Structure:



Other Names: Tilt®, Banner®, or CGA-64250®

Petitioner: Ciba-Geigy Corporation
P.O. Box 18300
Greensboro, North Carolina
Telephone (919)292-7100

Methods: Ciba-Geigy's Analytical Procedure, AG-454A, entitled "Determination of Total Residues of Propiconazole in Crops As 2,4-Dichlorobenzoic Acid By Capillary Gas Chromatography." The method is authored by Toth, J. and Manuli, P. J. of Ciba-Geigy, 36 pages, dated December 8, 1986.

Ciba-Geigy's Analytical Procedure, AG-517, entitled "Determination of Total Residues of Propiconazole in Meat, Milk and Eggs As 2,4-Dichlorobenzoic Acid By Capillary Gas Chromatography." The method is authored by Toth, J. and Manuli, P. J. of Ciba-Geigy, 43 pages, dated January 9, 1987.

Pesticide Petitions: 4F3074, 4F3007, and 4E3026.

Product Application: Method AG-454A for Crops (Wheat, barley, rice, rye, bananas, and pecans).

Method AG-517 for Livestock (meats, eggs, and milk).

Sensitivity: Method AG-454A: 0.05 ppm for wheat grain and pecan nutmeats; and 0.2 ppm for wheat straw.

Method AG-517: 0.05 ppm for beef liver and eggs; and 0.02 ppm for whole milk.

Method Trial Reports: Enclosed

Attachment 1. PAM II Cover Sheet (1 page).
Attachment 2. Method Trial Report Evaluation by RCB (4 pages).
Attachment 3. Ciba-Geigy's Analytical Method AG-454A (36 pages).
Attachment 4. Ciba-Geigy's Analytical Method AG-517 (43 pages).
Attachment 5. Method Trial Report for Method AG-454A from ECL/COB/BUD (14 pages).
Attachment 6. Method Trial Report for Method AG-517 from ECL/COB/BUD (12 pages).
Attachment 7. Method Trial Request for Method AG-454A (4 pages).
Attachment 8. Method Trial Request for Method AG-517 (4 pages).

cc [FDA letter (2 pages) plus Attachments 1 to 8]: M. Bradley.

cc [FDA letter (2 pages) plus Attachments 1 to 6]: A Marcotte (FDA) and Theresa Murtagh (PMSD/ISB/EPA).

bcc [FDA letter (2 pages) plus Attachment 1]: Circu, RF, S. Malak, SF (propiconazole or Tilt® or CGA-64250), PP#4F3074, PP#4F3007, PP#4E3026, Robert Thompson (RTP/NC), EAP, and Dean Hill (NEIC/ Denver)

RDI: P. V. Errico:5/15/87:R. D. Schmitt:5/15/87
TS-769C:RCB:CM#2:RM814A:S.Malak:X557-4379:4/30/87

Attachment 3

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

MAY 28 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4F3074, 4F3007, and 4E3026. Propiconazole (Tilt® or CGA-64250) on Crops and Livestock Commodities. Evaluation of Method Trial Report for Ciba-Geigy's Method AG454A and AG-517. No Accession or RCB Numbers.

FROM: Sami Malak, Ph.D., Chemist
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

TO: Lois Rossi, PM #21
Fungicide-Herbicide Branch
Registration Division (TS-767

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

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

Note: This method trial report is to be expedited at the request of the Registration Division's Director, Mr. E. F. Tinsworth (Letter of 3/4//87)

The Analytical Chemistry Laboratory of the Environmental Protection Agency (EPA) in Beltsville, Maryland reported to the Residue Chemistry Branch (RCB) on the method trial for Ciba-Geigy's fungicide, propiconazole (Tilt® or CGA-64250) on wheat grain, wheat straw, pecan nutmeats, beef liver, whole milk, and eggs (letter of Everette Greer, et al, 4/27/87). Ciba-Geigy's analytical procedure, AG-454A, entitled "Determination of Total Residues of Propiconazole in Crops As 2,4-Dichlorobenzoic Acid By Capillary Gas

Chromatography." The method is authored by Toth, J. and Manuli, P. J. of Ciba-Geigy, 36 pages, dated December 8, 1986. Also, Ciba-Geigy's analytical procedure, AG-517, entitled "Determination of Total Residues of Propiconazole in Meat, Milk and Eggs As 2,4-Dichlorobenzoic Acid By Capillary Gas Chromatography." The method is authored by Toth, J. and Manuli, P. J. of Ciba-Geigy, 43 pages, dated January 9, 1987.

Permanent tolerances are currently pending for residues of propiconazole (Tilt® or CGA-64250), 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole, in/on the grain of wheat, barley, rye, and rice at 0.1 ppm; straw of wheat, barley, and rye at 1.5 ppm; rice straw at 3 ppm; the kidney and liver of cattle, hogs, horses, sheep, and poultry at 0.1 ppm (PP#4F3074); pecan nutmeats at 0.1 ppm (PP#4F3007); and bananas at 0.2 ppm (PP#4E3026).

In the method trial of Method AG-454A, duplicate samples of wheat grain, wheat straw, and pecan nutmeats were fortified at 0.1 and 0.2 ppm for wheat grain and pecan nutmeats, and at 1.5 and 3 ppm for wheat straw.

In the method trial of Method AG-517, duplicate samples of beef liver, whole milk, and eggs were fortified at 0.1 and 0.2 ppm for beef liver; 0.02 and 0.04 ppm for whole milk,;and at 0.05 and 0.1 ppm for eggs.

Principles:

Method AG-454A for Crops:

Crop samples are extracted by refluxing with 20% concentrated ammonium hydroxide in methanol. Aliquots from the filtered extracts are evaporated to dryness, and the residues are converted to 2,4-dichlorobenzoic acid (DCBA) by heating with an alkaline permanganate solution. Excess permanganate is reacted with sodium meta-bisulfite and the solution is acidified with 6N HCL. After partitioning with 10% diethyl ether/hexane, the organic phase is evaporated to dryness, and the DCBA is derivatized with diazomethane. After an additional evaporation step, the residue is dissolved in hexane and cleaned up on an acidic alumina Sep-Pak. The DCBA is quantitated on a capillary GLC equipped with an electron detector.

In the method trial report, it was reported that a set of three samples require two days for analysis. Further, the method was modified by taking 9 ml sample aliquots instead of the 3 ml aliquots specified in the original method and the partition with diethylether/hexane is to be repeated twice for a total of three extractions (memo of Everett Greer, et, al, 4/27/87. These modifications allowed the GC to be run at a higher attenuation and reduced the effects of interference. These modifications were reported to Richard Conn of Ciba-Geigy on 4/29/87 who sent an updated version of the method (replaced pages 9 and 11 of the original method).

Method AG-517 for Livestock:

Livestock samples are mechanically extracted with 20% water/acetonitrile mixture. Aliquots from the filtered extracts are evaporated to dryness, and the residues are converted to 2,4-dichlorobenzoic acid (DCBA) by heating with an alkaline permanganate solution. Excess permanganate is reacted with sodium meta-bisulfite and the solution is acidified with 6N HCL. After partitioning with 10% diethyl ether/hexane, the organic phase is evaporated to dryness, and the DCBA is derivatized with diazomethane. After an additional evaporation step, the residue is dissolved in hexane and cleaned up on an acidic alumina Sep-Pak. The DCBA is quantitated on a capillary GLC equipped with an electron detector.

In the method trial report, it was reported that a set of three samples require two days for analysis. Further, the method was modified by taking 9 ml sample aliquots instead of the 3 ml aliquots specified in the original method (memo of Everett Greer, et al, 4/27/87). These modifications were reported to Richard Conn of Ciba-Geigy on 4/29/87 who sent an updated version of the method (replaced page 10 of the original method).

The petitioner responded to this on May 2, 1987 by submitting the necessary revisions to analytical methods AG-454A and AG-517. The original corrected pages replaced the corresponding pages in the previously submitted data package of these two methods.

The method, as modified, appears satisfactory for regulatory purposes for liver, milk, and eggs at the recommended tolerance levels.

Recoveries From Crop Samples BY Method AG-454:

The methodology gave recoveries ranging from 79 to 107%. Method sensitivity was reported at 0.05 ppm for wheat grain and pecan nutmeat; and at 0.2 ppm for wheat straw. Control values had residues less than sensitivity of the method.

Recoveries From Livestock Commodities By Method AG-517:

The methodology gave recoveries ranging from 75-110% for beef liver; 60-80% for whole milk; and 78-94% for eggs. Method sensitivity was reported at 0.05 ppm for liver and eggs; and at 0.02 ppm for whole milk. Control values had residues less than sensitivity of the method.

We conclude that adequate methodology for propiconazole (Tilt® or CGA-64250) in crops and livestock commodities are available for regulatory purposes. The methods may be incorporated in PAM II.

The correct and final method write-up will be forwarded to the Food and Drug Administration (FDA) for editing and publishing in PAM II and also to Mr. William Grosse, PMSD/ISB.

Therefore, a copy of the Analytical Methods for Propiconazole (Tilt® or CGA-64250) in crops and livestock commodities will be immediately available to State Laboratories, upon request, as cited in the Federal Register publication of the tolerances.

Recommendations

1. PP#4F3074:

   RCB continues to recommend against the requested tolerances for rice grain and straw, and small grains and their straws, pending resolution of deficiencies #1 and 3 stated under the Recommendations (subject petition, S. Malak, 5/14/87).

2. PP#4F3007 and 4E3026:

   TOX and EAB considerations permitting, RCB can now recommend for establishing the following requested permanent tolerances for residues of propiconazole:

   - PP#4F3007: 0.1 ppm for Pecans.
   - PP#4E3026: 0.2 ppm for bananas.

cc: Circu, RF. SF (propiconazole®, Banner®, or Tilt®),

S. Malak, PP#4F3007, PP#4F3074, PP#4E3026, PM #21, FDA (Alice Marcotte), and PMSD/ISB (Theresa Murtagh).

RDI: P. V. Errico:5/15/87:R. D. Schmitt:5/15/87
TS-769C:RCB:CM#2:RM814A:S.Malak:X557-4379:5/11/87.

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Reviewed by: Marcia van Gemert, Ph.D. Mvangemert 3/2/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C) 3/17/87

DATA EVALUATION REPORT

Study Type: Metabolism in rats

Tox. Chem No. 323EE

Accession No.: 265794

Test Material: CGA 64 250

Synonyms: Tilt, Technical

Study Number: 9/81

Sponsor: Ciba Geigy

Testing Facility: Dept. Research and Development, Plant Protection Agricultural Division, Ciba Geigy, Basle Switzerland

Title of Report: The major metabolic pathways of CGA 64 250 in the rat

Author: W. Mucke

Report Issued: March 13, 1981

Conclusions: This is an extension of the previously reviewed study where ^{14}C- CGA 64 250 was given in a single gavage dose and was extensively metabolized in the rat with no detectable parent compound in urine and about 5% found in feces after 3 days.
The major metabolic pathways in this study have been proposed for CGA 64 250 based on NMR and mass spectroscopy analyses. A major metabolic pathway is through cleavage of the dioxalone ring with subsequent dechlorination and conjugation.

Core Classification: minimum

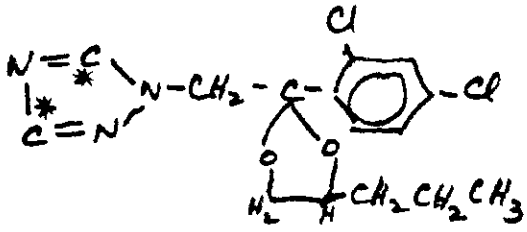
Quality Assurance Statement accompanied the report and was signed.

A. Materials:

1. Test Compound: Radiolabelled compounds used.

A. Triazole [3,5-^{14}C] CGA 64 250 (triazole labelled)

Structure:



Specific Activity: 59.6 uCi/mg

Isomer ratio: 49.4% trans
50.6% cis

Purity: > 98%

This material was diluted with unlabelled CGA 64 250 with the following characteristics:

Isomer ratio: 39.5% trans
60.5% cis
purity: 98.9%

to yield a specific activity of 23.1 uCi/mg

2. Test Animals:
Species: rats, male
Strain: Tif: RAI f(spf)
Weight: 167-186 gms
Age: not given
Source: Ciba Geigy Farms, Stein, Switzerland

3. Dosing solution: Given by gavage, dissolved in water/ethanol/ polyethylene glycol 200 (50/30/20 v/v)
Triazole labelled CGA 64 250 - 5.5 mg/ml
phenyl labelled CGA 64 250- 5.78 mg/0.9 ml

4. Animal assignments and study procedures:
20 male rats were treated orally with a single dose of 31.4 mg/kg triazole labelled CGA 64 250 and urine and fecal excretion of radioacctivity were determined.

Results:
The major results of this study are given in the previously reviewed metabolism study # 35/79 dated Aug. 31, 1979. This study gives some of the proposed metabolic pathways apparent from NMR and mass spectroscopy analyses.
A summary of the excreted radioactivity is on appended page 1.
Approximately 52.3% of the total radioactivity was excreted in urine by 3 days, 43.3% in feces giving a total excreted of 95.6%.

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CASWELL FILE

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

MAR 18 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Review of submitted studies on Tilt

To: Lois Rossi, PM-21
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED
M van Gemert 3/11/87

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED

Chemical: CGA- 64 250, Tilt

Project No: 7-0227

Caswell No: 323EE

Record No: 185584

3/17/87

Action Requested: Review incoming data.

Comments:

A list of the studies submitted is enclosed and summarized below, along with the conclusions reached on each study. Concerning the metabolism studies, when taken as a whole, they appear to adequately cover the requirements for metabolism. It would have been important to do a repeat radioactive-dose study measuring radioactivity in tissues at various time periods to estimate tissue half-lives and potential bioaccumulation. However, the Toxicology guidelines concerning metabolism requirements are not sufficiently well stated to insist on this study at this time. Furthermore, judging from the information presented in this submission, bioaccumulation will probably not be a problem with this chemical.

1. Metabolism of CGA 64 250 in the rat. Study # 24/83, Sept. 1, 1983.
A single oral dose of 31.4 mg/kg ^{14}C-CGA 64 250 was administered by gavage to an unspecified number of rats. Urine and feces were collected for 3 days and analyzed. The major metabolic route taken by CGA 64 250 is by enzymatic attack of the propyl side chain and cleavage of the dioxolane ring. The phenyl ring is attacked by formation of a cyclohexadiene ring. Hydroxylation replacement of one of the chlorines by a hydroxyl group and

introduction of a methylthio group. The triazole ring can be oxidatively attacked to form hydroxy-derivatives. Most of the alcoholic, phenolic, sulfuric acid and glucuronic acid conjugates are excreted in the urine.

Core classification: minimum

2. Distribution, degradation and excretion of CGA 64 250 in the rat. # 24/79, July 18, 1979.
2 animals/sex were given a single dose of 0.5 mg/kg or 25 mg/kg ^{14}C CGA 64 250. Urine, feces and expired CO_2 were collected at 24 hour intervals for 6 days post dosing, after which animals were killed and tissues collected for analysis. Administered ^{14}C appeared to be rapidly excreted in the urine. Very little radioactivity was recovered from expired CO_2. Most tissue residue levels were extremely low, except for liver and kidneys in males and females and ovaries in females. Urinary metabolite pattern of the 0-24 hour urines appeared similar for both sexes and both doses. There were 4-10 polar metabolites detected in urine with no detectable intact parent compound found (cis or trans).
Core Classification: supplementary

3. Characterization of urinary and fecal metabolites of rats after oral application of CGA 64 250. # 35/79, Aug. 31, 1979.
^{14}C-CGA 64 250 when given in a single gavage dose is extensively metabolized in the rat with no detectable parent compound in urine and about 5% found in feces after 3 days. About 80% of the urinary metabolites are acidic and fecal metabolites are somewhat less polar. Only 12 and 9% of urinary metabolites are susceptable to aryl sulfatase and b-glucuronidase respectively. There is evidence in urine and fecal metabolites that some metabolism is through cleavage of the dioxolane ring. However, two labels were used, one in the triazole and the other in the phenyl ring and very similar excretion patterns of these two would indicate that in most metabolites the bridge between the phenyl and the triazole ring remains intact.
Core Classification: minimum

4. Dermal absorption of ^{14}C propiconazole. # ABR-86064, 9/30/86.
Three groups of 4 male rats/group were treated with dermal application of ^{14}C propiconazole. One group was treated for 24 hours and immediately sacrificed, a second group was treated for 10 hours, the skin washed with soap and water rinse followed by 72 hours of depletion time after a soap and water rinse. Dose levels used were 0.1, 1.0 and 10.0 mg/rat. For the 24 hour exposed rats the percent absorbed was 57.1, 27.1 and 30.1% for the low, mid and high dose groups respectively. The rate of excretion of radioactivity was inversely related to the dose administered. For the 10 hour exposure (72 hour depletion) animals the dose absorbed was 42.4, 21.5 and 31.0% of the administered radioactive dose for the low, mid and high dose groups respectively. For the 24 hour exposure (72 hour depletion) animals the dose absorbed was 54.7, 29.8, and 29.8% of the dose administered for the low, mid and high dose groups respectively. Both groups of animals which had

depletion times excreted the bulk of the radioactivity within 24 and/or 48 hours, mainly in the urine. Results suggest that the radioactivity remaining in skin after 72 hours is somehow bound and is not available for further absorption.
Core Classification acceptable

5. Dermal absorption of ^{14}C-propiconazole in rats after a 10-hour exposure period. # ABR 86053, 8/4/86.
4 male rats/time point and 12/treatment level were given 0.1, 1.0 or 10.0 mg/rat. Treated rats were sacrificed at 2, 4 and 10 hours after skin application. The rate of absorption from skin was inversely proportional to the dose administered. The percent absorbed after 10 hours exposure was 54, 36 and 29% of the administered dose for the low, medium and high dose groups respectively. Most of the remaining radioactivity remained either on or in the skin, with total skin residues of 45.9, 78.8 and 60.2% for low, medium and high dose groups respectively.
Core classification: acceptable

6. Effect of repeated oral administration of CGA 64 250 on liver weight of male and female mice. # 12/86, Aug. 20, 1986.
Male and female mice were fed unlabeled CGA 64 250 for 21 days at doses of 5, 100, 2500 ppm CGA 64 250 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level. Liver weights were recorded 4 days post ^{14}C dosing and were significantly increased in the high dose (2500 ppm) males and females. When presented as liver/body weight ratios, data for both males and females showed an increase in the high dose. A female animal treated with a single dose (equivalent to a daily dietary dose of 2500 ppm) only of ^{14}C-CGA 64 250 also showed an increase in absolute and relative liver weights.
Core Classification: supplementary

✓ 7. The major metabolic pathways of CGA 64 250 in the rat. #9/81, March 13, 1981.
This is an extension of the previously reviewed study where ^{14}C-CGA 64 250 was given in a single gavage dose and was extensively metabolized in the rat with no detectable parent compound found in urine and about 5% found in feces after 3 days. The major metabolic pathways in this study have been proposed for CGA 64 250 based on NMR and mass spectroscopy analyses. A major metabolic pathway is through cleavage of the dioxolane ring with subsequent dechlorination and conjugation.
Core Classification: minimum

8. The metabolism of [U-^{14}C] phenyl CGA 64 250 in mice after pretreatment with unlabeled CGA 64 250. # 12RB01,02,03,(PR 6/86) May 20, 1986.
Male and female mice and male rats were fed unlabeled Tilt for 21 days at doses of 5, 100, 2500 ppm CGA 64 250 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level. Mice eliminate a major portion of the radioactivity in urine, with males excreting a greater percent than females.

Rats excreted equal amounts in both urine and feces. Four days post dosing with ^{14}C CGA 64 250 residues remained in liver, kidneys and carcass in mice and liver in rats. The predominant urinary metabolite in mice was the glucuronic acid conjugate of the metabolite CGA 91 305. The predominant metabolic pathway in mice involves the dioxolane ring cleavage.
Core classification: minimum

9. A teratology study in New Zealand White Rabbits. # 86043 (MIN 852172) Aug. 1, 1986.
Groups (19/group) of pregnant rabbits were administered CGA 64 250 at doses of 100, 250 and 400 mg/kg from gestation days 7 through 19. AT 250 and 400 mg/kg, the treated animals showed decreased food consumption and body weight gain during the treatment period. At 400 mg/kg, treated rabbits also showed increased incidence of abortion. There was, however, no evidence of developmental toxicity.
Based upon the data, the NOEL for maternal toxicity was estimated to be 100 mg/kg; LEL, 250 mg/kg. The NOEL for developmental toxicity was estimated to be 400 mg/kg (HDT).
Core Classification: supplementary. The report must contain the data on the animals which were sacrificed before the termination of the study, specifically those rabbits which had aborted or delivered early in the study.

Reviewed by: Marcia van Gemert, Ph.D. MvanGemert 3/9/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Metabolism in rat Tox. Chem No. 323EE

Accession No.: 265794

Test Material: CGA 64 250 fungicide

Synonyms: Tilt, propiconazole

Study Number: 12RB01, 12RB02, 12RB03 (PR 6/86)

Sponsor: Ciba Geigy

Testing Facility: Ciba Geigy Agricultural Division, Basle Switzerland

Title of Report: The metabolism of [U-^{14}C]-phenyl CGA 65250 in mice after pretreatment with unlabelled CGA 64 250

Author: R. Bissig

Report Issued: May 20, 1986

Conclusions: Male and female mice and male rats were fed unlabeled Tilt for 21 days at doses of 5, 100, 2500 ppm CGA 54 250 followed by a single oral dose of ^{14}C CGA 64 250 at the corresponding dose level. Mice eliminate a major portion of the radioactivity in urine, with males excreting a greater percent than females. Rats excreted equal amounts in both urine and feces. Four days post dosing with ^{14}C-CGA 642500 residues remained in liver, kidneys and carcass in mice and liver in rats. The predominant urinary metabolite in mice was the glucuronic acid conjugate of the metabolite CGA 91 305. The predominant metabolic pathway in mice involves the dioxolane ring cleavage.

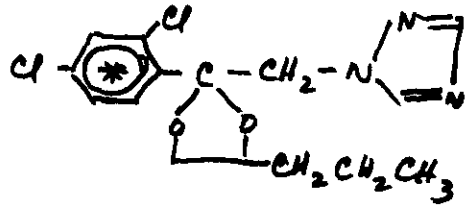
Core Classification: minimum

Quality Assurance Statement accompanied the report and was signed.

A. Materials:

1. Test Compound:

Description: Labelled compound: Specific Activity = 56.9uCi/mg
Batch: GAN-VI-43
Supplier: H. Mory, N. Wigger
Purity: 92%, increased to 97% via column chromatography
Cis/trans ratio: 49/51 (determined by TLC)
Structure:



Description: Unlabelled Compound:
Batch: OP 412127,
Purity: 91.1%
Cis/trans ratio: 59/41
Dilution of labelled compound to a specific activity of 18.9 uCi/mg and 17.8 uCi/mg for males and females respectively.

2. Test Animals:

Species: Mice

Strain: CD-1

Age: 4 weeks

Weight:22-26 gms

Source: Charles River WIGA, GmbH, Switzerland, Germany

Species: Rat

Strain: Tif:RAI F (SPF)

Age: 7 weeks

Weight: 200 gms

Source: Animal Production Stein, Ciba Geigy

Study Design:

Animal assignments and study procedures:

Mice: 21 males (7/dose level) and 24 females (7/dose level at end of study). 2/sex were used as control. After dosing animals were kept in glass metabolism cages. Food containing the radioactive

CGA 64 250 and water were given ad libitum except the evening before ^{14}C- test compound administration. After ^{14}C dosing animals were allowed food and water ad libitum. Urine and feces were collected at 24 hour intervals. 4 days post ^{14}C-dosing animals were killed and blood, liver. kidneys, lungs and remaining carcass were analyzed. Body weights were taken at weekly intervals.

Rats: 3 male rats were used, one served as control. Food and water were given ad libitum except 19 hours pre ^{14}C dosing, when animals were fasted. Urine and feces were collected at 24 hour intervals. Animals were killed 4 days post ^{14}C dosing and blood, liver, kidneys, lungs and remaining carcass were taken for analysis. Body weights were taken at start and end of the experiment.

Test Procedure:

Test material was mixed in the diet and given for 21 days. Test doses were 5, 100 and 2500 ppm. ^{14}C CGA 64 2500 was dissolved in ethanol/ polyethylene glycol 200/water (7/9/4 v/v). Dosing solution was 0.1 and 0.4 ml by stomach tube for mice and rats respectively. Labelled ^{14}C CGA 642500 was equivalent to 5, 100 and 2500 ppm in the 24 hour food assuming a daily consumption of 5 gms for mice and 20 gms for rats consumed per day.

Measurement of radioactivity is on appended pages 1-4. Procedures for thin layer chromatography, liquid chromatography, high performance liquid chromatography, spectroscopic methods, enzymatic hydrolysis and calculations are on appended pages 4-12.

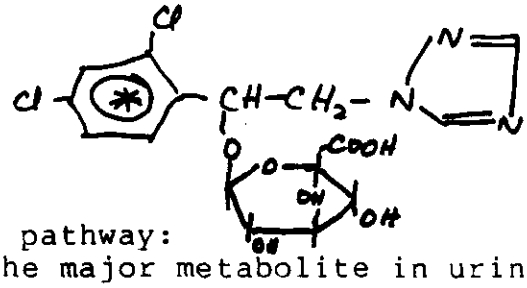
Results:

The 3 female mice given a bolus dose of 600 mg/kg ^{14}C-CGA 64 250 without pretreatment of unlabelled compound showed severe signs of toxicity and two died 48 to 72 hours post dosing.

Excretion:
Within 24 hours mice excreted 64% of the dose administered and rats excreted 94%. Major excretory route for mice with 45-81% excreted in urine and 22-43% excreted in feces by 96 hours was urine, while in rats, urine was 48% and feces 54% of the excreted radioactive dose. There is a slight difference in excretion pattern between sexes in mice.

Tissue residues:
Tissue residue data are on appended page 14. The highest residue levels appear to be in the liver and carcass for the male and female mice. Rat liver appeared to accumulate only about 10% (0.2245 ppm) of the residue levels found in mice (2.262 ppm for males and 2.956 ppm for females) and the carcass of the rat retained very little radioactivity. The residues in female mice were 1.3 to 2.2 times higher than males at all dose levels with respect to blood, liver, lungs and carcass (except for a 0.6 ratio in carcass in the 5 ppm treatment groups). Residues in the kidney were up to 5 times greater in males than in females.

Urinary metabolites·
Two dimensional TLC revealed 15-30 metabolites in 0-24 hour urines. There are sex and species differences in metabolites. Appended page 15 details the quantitative distribution of these metabolites. The most significant metabolite to show sex and species differences is metabolite U_2 which was 61-73% in male mice, 29-41% in female mice and 6% in male rats.
The U_{12} fraction was another example of sex and species as well as dosage difference in metabolic excretion products. At 5 and 100 ppm female mice and rats excreted more of the U_{12} metabolite whereas male mice and female mice at the 2500 ppm dose level excreted only 2-7% of this fraction. In an earlier study this metabolite was identified as a-hydroxy-carboxyacid (metC_U) See appended page 16 for structure.
According to the study text if mouse urines are incubated with b-glucuronidase then 75-85% of the U_2 fraction disappears giving rise to a more unpolar U_{18} fraction. In rat urine, however, the most polar fraction U_1 completely disappears after b-glucuronidase incubation and forms several unpolar fractions. The u_2 fraction is not significantly affected. The study authors conclude that there is some unique glucuronide conjugation inherent in the mouse.
The study text stated that incubation of the urines with aryl sulfatase did not significantly change the metabolite pattern.
The study text further stated that U_{18} fraction consisted of at least 2 compounds, one was the alcohol CGA 91 305, the structure of which can be found on appended page 16 and is the exacon of the major metabolite fraction U_2 in mice urines. The second major component of U_{18} was the analogous ketone CGA 91 304. (structure on appended page 16). The major urine metabolite isolated from the U_2 fraction was determined to be Met IU, the glucuronic acid conjugate of the metabolite CGA 91 305. The structure is elucidated below:



Metabolic pathway:
In mice the major metabolite in urine, regardless of sex, dose level and pretreatment, is the glucuronic acid conjugate of the metabolite CGA 91 305 with the structure above (Met IU).
The study text states that this implies that the major metabolic pathway in mice proceeds via elimination of the dioxolane ring leading via ketone formation (CGA 91 304) to the corresponding acid to yield IU. In males this represents 30% of the dose, whereas in females, this is 15% of the dose administered.

In rats the unpolar metabolite fractions U_{15} through U_{18} represent metabolites where the dioxolane ring had been cleaved. In summary mice cleave the dioxolane ring to a higher extent (70 and 40% for males and females) than do male rats (30%).

Discussion:
Male and female mice and rats were fed the unlabeled tilt for 21 days doses of 5, 100 or 2500 ppm CGA 64 2500 followed by a single oral dose of $_{14}$C CGA 64 250 at the corresponding dose level.

Mice eliminate a major portion of radioactivity in urine, with males excreting a greater percent than females. Rats excreted equal amounts in both urine and feces. Four days post dosing with ^{14}C CGA 64 250 residues remained in liver kidneys and carcass in mice and liver in rats.
The predominant urinary metabolite in mice was the glucuronic acid conjugate of the metabolite CGA 91 305. The predominant metabolic pathway in mice involves the dioxolane ring cleavage.

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

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

AUG 5 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: PP No. 9F3706. Propiconazole on Grass Seed Screenings, Straw, and Forage. Ciba-Geigy Request for Guidance on Residue Data Requirements. No MRID Number. CB No. 7759. HED Project No. 1-0840. DP Bar Code No. D162311.

FROM: Stephanie H. Willett, Chemist
Tolerance Petition Section 2
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

THRU: Richard Schmitt, PhD, Branch Chief
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

TO: Susan Lewis/Jim Stone, PM Team 21
Registration Division (H7505C)
and
Toxicology Branch-HFA Support
Health Effects Division (H7509C)

Background

Tolerances with expiration dates have been established for the residues of propiconazole on grass forage, straw and seed screenings at levels ranging from 0.5 to 10 ppm. Additional field trial data are needed to support permanent tolerances (see memo of H. Fonouni dated 2/7/89). Some data were submitted, but were determined to be inadequate since application of the pesticide was not made according to label directions, and there was a significant amount of residue in the control samples (see PP No. 1F3974, memo of S. Willett dated 6/11/91).

Ciba-Geigy is planning to repeat the field trials in accordance with label directions. However, since residue levels from aerial applications were lower than those from ground applications in the previous field trials, the company is asking if it is necessary to repeat the aerial application portion of the study (see letter dated March 1, 1991 from Dennis Hacket). The company's comparison of aerial vs. ground residues is summarized in the following table (see also S. Willett memo dated 6/11/91).

COMPARISON OF MAXIMUM TOTAL RESIDUES OF PROPICONAZOLE IN GRASS SUBSTRATES FOLLOWING EITHER GROUND OR AERIAL APPLICATION OF TILT 3.6E AT THE 1X TREATMENT RATE

Field Test	Substrate	Aerial App.	Ground App.
OW-FR-129-89	Seed	0.45	29
	Straw	23	30
	Screenings	1.6	43
	Forage	1.0	0.75
OW-FR-130-89	Seed	21	35
	Straw	13	36
	Screenings	37	67
	Forage	0.42	0.59
OW-FR-617-89	Seed	8.2	23
	Straw	4.5	18
	Screenings	21	60
	Forage	0.06	0.06

CBTS Comments

CBTS did agree that the residue levels from aerial application appeared lower than those from ground application based on the previously submitted data. However, since the data are not considered completely reliable because of the high level of residues found in the controls samples (see PP No. 1F3974), the petitioner should conduct at least one additional trial where the pesticide is applied using aerial equipment. This will insure that the previous observations are correct, and leave no room to question the validity of the residue data.

cc: PP Nos. 1F3974, 9F3706, Willett, Circ, E. Haeberer,
PIB/FOD (C. Furlow)
CM2:H7509C:RM803A:X1439:SHWillett:shw-7/18/91
RDI: E. Haeberer, 7/31/91; R. Loranger, 7/31/91

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

JUN 11 1991

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EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP No. 1F3974. Propiconazole on Grass Seed Screenings, Straw, and Forage. Evaluation of Residue Data and Analytical Methodology. MRID Nos. 41823300, -05. CB No. 7822. HED Project No. 1-0964. DP Bar Code No. 1-0964.

FROM: Stephanie H. Willett, Chemist
Tolerance Petition Section 2
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

THRU: Richard Schmitt, PhD, Branch Chief
Chemistry Branch I-Tolerance Support
Health Effects Division (H7509C)

TO: Susan Lewis/Jim Stone, PM Team 21
Registration Division (H7505C)
and
Toxicology Branch-HFA Support
Health Effects Division (H7509C)

Ciba-Geigy is requesting the establishment of new tolerances for propiconazole on grass seed screenings, straw and forage at 70, 40 and 2 ppm, respectively, in the subject petition. Propiconazole (TILT ®) is a broad spectrum fungicide used to control rusts, powdery mildew, and Selenophoma stem eyespot in grasses grown for seed. Interim tolerances for these animal feed items were established at 10 to 0.5 ppm in PP No. 9F3706, but will expire on June 21, 1991. The 2.0 ppm tolerance on liver and kidney of cattle, goats, horses and sheep will also expire on this date.

Tolerances for propiconazole, 1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl] methyl}1H-1,2,4-triazole and its metabolites, determined as 2,4-dichlorobenzoic acid, expressed as parent compound equivalents, are published in 40 CFR 180.434 on several commodities, including bananas, pecans, wheat, barley, rice, and rye. Several other tolerances are pending.

Propiconazole is a list C chemical, and is subject to reregistration requirements (see review of J. Smith dated 6/15/90).

Conclusions

1. The product chemistry for technical grade propiconazole and the TILT 3.6E formulation have been adequately described.

2. The use on grass grown for seed has been adequately described.

3. The metabolism of propiconazole in plants has been adequately delineated.

4a. CBTS will withhold its decision on the adequacy of the ruminant metabolism study until we can determine appropriate tolerances for grass seed screenings, straw and forage, and subsequently better estimate the dietary burden to cattle. Additional characterization of residues in liver and kidney may be necessary if the residue levels in the feed items approach those used in the metabolism study (67 to 90 ppm).

4b. The petitioner should provide details on the handling of ruminant metabolism study samples and length of storage, and submit or reference storage stability data.

5a. The poultry metabolism study is generally acceptable. However, CBTS will withhold its final conclusions on the adequacy of the study until it can be considered in the context of the petitions to which it is relevant (i.e. tolerance petitions on corn and peanuts). Since no poultry feed items are associated with the use on grass seed, the establishment of appropriate tolerances is not contingent upon the adequate delineation of the metabolism of propiconazole in poultry.

5b. We note that no details on sample handling and length of storage were supplied, and no data from storage stability studies on animal commodities were submitted or referenced. This information will be needed to insure sample integrity when considering the relevant petitions.

6. Since the enforcement methodology for crops and animal commodities is capable of quantifying propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety, CBTS concludes that enforcement methodology is adequate.

7. The residue data do not simulate the label use since the application intervals were shorter, and the PHI shorter than specified on the label. Also, there was a significant amount of residue in the control samples, indicating possible misconduct of the trials. The residue data are therefore inadequate, and CBTS cannot recommend for the establishment of new tolerances based on these data.

8. CBTS will withhold its final conclusions on the adequacy of the tolerances on meat and milk until additional residue data are submitted and adequate tolerance levels for grass seed screenings, straw and forage can be determined.

Recommendations

CBTS recommends against the establishment of tolerances for grass seed screenings, straw and forage at 70, 40 and 2 ppm for reasons outlined in conclusions 4a, 4b, 7 and 8 above. However, because of the extenuating circumstances that continue in the northwest, and the limited use on grass seed, CBTS has no objection to extending the interim tolerances for seed screenings, straw and forage at 10, 5 and 0.5 ppm, and livestock liver and kidney until these deficiencies can be resolved. Limited data are available in support of the interim tolerances. Additional data are forthcoming.

Detailed Considerations

Product Chemistry

The manufacturing process of technical grade propiconazole has been previously described. The technical grade product is approximately 88% pure. The impurities are not of concern at the levels which are likely to be present (see PP No 4F3007, 5/15/84 memo of A. Smith).

The formulation used on grass is TILT^{R} 3.6E, which contains 3.6 lb ai/gal (EPA Reg. No. 100-617). The inert ingredients in the formulation have been cleared under 40 CFR 180.1001.

Proposed Use

The proposed use remains unchanged from that which was previously reviewed in PP No. 9F3706 (see also 2/7/89 memo of H. Fonouni).

TILT is used to control rusts, powdery mildew, and Selenophoma stem eyespot in grasses grown for seed, such as perennial ryegrass, fescue, bluegrass, orchardgrass and wheatgrass **only in Nebraska, Oregon, Washington, Idaho and Minnesota**. The label specifies an application rate of 4 to 8 fl. oz. of the formulation in 20 gallons of water/A (ground), or 10 gallon/A (aerial). Application begins with observation of infestation, with subsequent applications in 14 to 21 day intervals. The maximum application rate is 32 fl. oz. formulation/A/growing season, or approximately 400 g ai/A/growing season. A minimum PHI of 20 days is specified.

The label also prohibits feeding of hay cut within 20 days of last application, and grazing of treated areas within 140 days of last application. These restrictions imply that use on pastureland grass is prohibited.

The use has been adequately described.

Plant Metabolism

The metabolism of propiconazole has been studied in wheat, corn, peanuts, grapes, lettuce, carrots and tomatoes (see PP No. 4F3007, 5/15/84 memo of A. Smith). The plant residues are comprised of the parent compound, free and sugar-conjugated hydroxy metabolites with the intact parent ring system (dichlorophenyl, triazole, and dioxolane) and others without the dioxolane ring portion.

The data adequately support the use on grass grown for seed. The regulated residues are the parent and its metabolites containing the 2,4-dichlorophenyl moiety (see discussion under analytical methodology). The Toxicology Branch has concluded that there is no need to specifically regulate the triazole metabolites (see DEB memo of S. Malak dated 5/14/87 and TOX memo of A. Katz dated 5/8/87).

Ruminant Metabolism

A ruminant metabolism study was previously conducted where lactating goats were fed triazole labeled propiconazole at 4.53 ppm in feed for 10 days (see also 5/15/84 memo of A. Smith). Approximately 90% of the activity was excreted in urine and feces. The maximum residue levels in milk, liver, kidney, fat and muscle were .015 ppm, .096 ppm, .029 ppm, .008 ppm and .01 ppm, respectively. Characterization of milk and liver residues showed no parent compound present. The residues in milk consisted of sulfate and glucuronide conjugates and components containing the triazole ring. The residues in milk did not preferentially transfer to fat. Characterization of the liver residues showed that 80 to 90% of the activity is triazole metabolites conjugated with amino acids and/or bound to proteins by peptide bonds.

In PP No. 9F3706, it was concluded that due to the possibility of significant dietary burden cattle resulting from this use, additional ruminant metabolism study data would be needed where more of the activity was characterized before permanent tolerances could be established (see memo of H. Fonouni dated 2/7/89). This requirement was also specified in conjunction with the pending tolerances on peanuts (PP No. 8F3654) and corn (PP No. 8F3674).

A new ruminant metabolism study was submitted in support of this petition (MRID No.41823301). Two lactating goats received a daily

oral dose of 125 mg of phenyl ^{14}C propiconazole for four consecutive days, equivalent to approximately 67 to 92 ppm in feed. Samples of milk, urine, and feces were collected daily, including predose days -2 and -1. Six hours after the last dose, the goats were sacrificed and tissue samples taken. Samples were stored frozen at -20°C until analyzed. An untreated goat was also sacrificed.

The majority of the radioactivity was eliminated in urine and feces in 4 days (71.7 to 81.6%). Subsamples of tissues and milk were analyzed for total radiocarbon content by LSC/combustion. The total radioactivity was reported as follows:

TABLE 1. SUMMARY OF ^{14}C-PROPICONAZOLE RESIDUE LEVELS FOUND IN GOAT TISSUES AND MILK (ppm)[1]

	Goat		
Tissue	#73	#74	Average
Liver	4.52	3.14	3.83
Gall Bladder	4.45	1.51	2.98
Kidney	2.67	2.38	2.53
Blood	0.33	0.27	0.30
Heart	0.13	0.18	0.15
Tenderloin Muscle	0.08	0.08	0.08
Leg Muscle	0.07	0.08	0.08
Omental Fat	0.07	0.09	0.09
Perirenal Fat	0.06	0.10	0.08
Milk, day 4	0.23	0.21	0.22

1 - Calculated as ppm of propiconazole

For metabolite characterization, activity from selected samples of liver, kidney and tenderloin was extracted with acetonitrile, followed by water. The ACN and water extracts were counted separately by LSC. The remaining solid pellet was weighed and aliquots taken for combustion/LSC analysis. Omental fat was extracted with hexane, and water. Milk was extracted with ethyl acetate, and acetonitrile. The majority of the activity was extractable (93 to 98%, corrected for recovery).

The tissue and milk **organic phase extracts** (75 to 93% of activity) were analyzed by TLC and HPLC. Qualitative TLC analysis in $CHCl_3$:isopropanol indicated the presence of up to 3 compounds (milk not analyzed by TLC). Samples were filtered and concentrated prior to analysis by solvent gradient HPLC. Milk acetonitrile extracts were subjected to enzymatic hydrolysis using beta-glucuronidase and aryl sulfatase prior to HPLC analysis. Analysis of this extract revealed that the radioactive residues were resistent to hydrolysis by beta-glucuronidase. However hydrolysis of polar milk residues with aryl sulfatase produced compounds that appeared less polar on reverse-phase HPLC, suggesting the presence of sulfate conjugates of ring-hydroxylated species.

The compounds were identified by comparison to standards using TLC, HPLC and/or GC/MS (HPLC/MS for milk samples). Component A was identified as propiconazole parent. Components B and C as CGA-188244 and CGA-91305, respectively (see page 8). "Metabolite D" is believed to consist of several components, and was not further characterized. Metabolites E-G were present only in milk ACN extracts. Attempts were made to isolate milk components by HPLC and characterize their mass spectra. Due to low levels of these components, exact identification was not possible. These components appeared to be aryl sulfate conjugates based on their chromatographic behavior after treatment with aryl sulfatase, and are probably closely related in structure (possibly enantiomers).

Water extractable ^{14}C-components from liver and kidney of both goats were also characterized by TLC also using $CHCl_3$:isopropanol. Components A and B were identified. However, 68 to 70% of the activity was highly polar, remained at the origin of the TLC plate, but was not identified. Similarly, in kidney, a component with an Rf similar to that of propiconazole was detected in extracts from both animals was found to represent 6 to 7.5% of the extracted radiocarbon. Most of the extracted activity (60 to 63%) remained at the origin of the TLC plates, and was not identified. No results of the characterization of water extractable activity in tenderloin muscle and omental fat were reported. No attempt was made to characterize the unextracted activity (<5% of TRR).

The following table summarizes the results of the goat metabolism study.

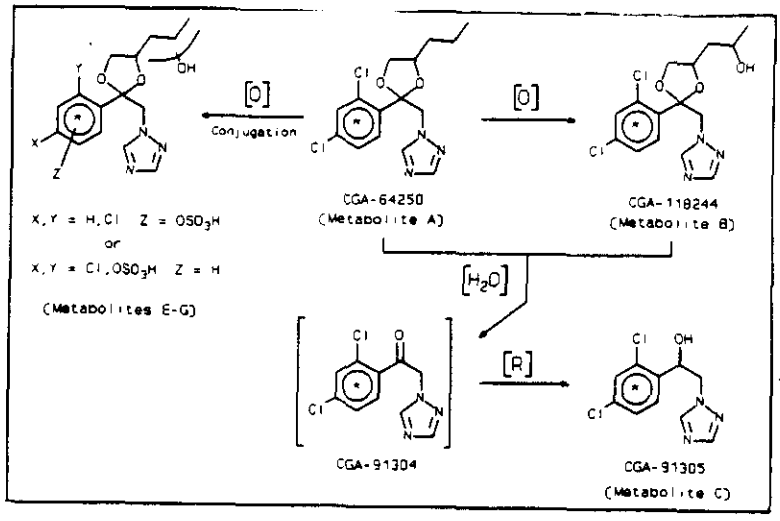
TABLE 2. CHARACTERIZATION OF 14C RESIDUES IN GOAT TISSUE AND MILK FED PROPICONAZOLE

Tissue[2] Total ppm	Component, ppm (%)[1] A	B	C	D	E	F	G	Total ID[3] ppm (%)
Liver 4.52 ppm	.63 (13.9)	.95 (21.0)	.72 (15.9)	.67 (14.8)				2.3 (51)
Kidney 2.67 ppm	.12 (4.5)	.25 (9.4)	.47 (17.6)	.83 (31.1)				.84 (32)
Muscle .08 ppm	.0014 (1.7)	.011 (13.4)	.024 (30.3)	.015 (19.2)				.04 (50)
Omental Fat .07 ppm	.014 (20.3)	.024 (34.0)	.022 (31.3)					.06 (86)
Milk .21 ppm		.049 (23.3)	.051 (24.3)	.013 (6.2)	.011 (5.2)	.013 (6.2)	.024 (11.4)	.11 (52)

1 Calculated as propiconazole
2 Total ppm determined by combustion/LSC
3 A+B+C

Computer generated images of TLC plates and HPLC chromatograms of standards and treated samples were provided.

The following metabolic pathway has been proposed by the petitioner. Metabolites B and C result from hydroxylation of the propyl side chain and deketalization/reduction, respectively, and experimental results indicate possible de-chlorination and/or aryl sulfate conjugation.



CBTS Comments/Conclusions, re: Ruminant Metabolism

CBTS will withhold its decision on the adequacy of the ruminant metabolism study until we can determine appropriate tolerances for grass seed screenings, straw and forage, and subsequently better estimate the dietary burden to cattle. Additional characterization of residues in liver and kidney may be necessary if the residue levels in the feed items approach those used in the metabolism study (67 to 90 ppm). Grass straw, seed screenings and forage may contribute significantly to the cattle diet ($\leq$ 75%). Generally, CBTS requires complete characterization of extractable radioactive residues which are present at levels of 0.05 ppm or above.

Additionally, no details on sample handling and length of storage were supplied, and no data from storage stability studies on animal commodities were submitted or referenced. This information is needed to insure sample integrity.

Poultry Metabolism (MRID No. 41823302)

No poultry metabolism studies have been previously submitted. Grass seed screenings, hay and forage are not poultry feed items and therefore the results of this study have no impact on establishment of the tolerances proposed in this petition. Since these data are relevant to the pending tolerances on peanuts and

corn (PP Nos. 8F3654, 8F3674) and were included in this submission, the study will be briefly discussed here.

Four laying hens were dosed daily with 10 mg of ^{14}C-phenyl labeled propiconazole for 8 consecutive days, equivalent to about 67 ppm in feed based on 150 g feed/day intake. A fifth hen served as a control. Six hours after the last dose, all hens were sacrificed. Samples of breast muscle, thigh muscle, gizzard, crop, heart, liver, kidney, skin and attached fat, peritoneal fat pad, and blood were taken at the time of sacrifice. Samples of eggs and excreta were taken prior to dosing and throughout the study. All samples were stored at -20^{0}C until analyzed. Total radioactivity was determined by LSC/combustion. The following summarizes the data submitted.

TABLE 3. TOTAL ^{14}C-PROPICONAZOLE LEVELS[1] FOUND IN POULTRY TISSUES AND EGGS

	Animal				
Tissue	#78	#84	#87	#91	Average
Kidney	5.27	4.40	3.33	3.74	4.19
Liver	4.98	4.07	3.24	3.45	3.94
Gizzard	3.75	2.73	1.20	1.83	2.38
Crop	4.51	2.68	1.03	0.92	2.28
Peri. Fat	1.05	1.02	1.11	0.72	0.98
Heart	0.92	0.83	0.56	0.52	0.71
Blood	0.96	0.79	0.53	0.47	0.69
Skin/fat	0.66	0.68	0.56	0.47	0.59
Thigh Muscle	0.59	0.42	0.32	0.26	0.40
Breast Muscle	0.46	0.36	0.28	0.23	0.33
Egg Whites[2]	0.34	0.23	0.95	1.26	0.70
Egg Yolk[3]	2.08	1.50	No sample	1.44	1.67

1 Calculated as ppm propiconazole
2 maximum levels, which occurred on day 5
3 maximum levels, which occurred on day 7

From 73 to 87% of the administered activity was eliminated in the excreta. For residue characterization and identification, radioactivity from selected ground tissue samples was extracted

using acetonitrile, followed by water. The ACN and water extracts were counted separately by LSC. The remaining solids pellet was weighed and aliquots taken for combustion/LSC analysis. Egg white and egg yolk were extracted separately with acetonitrile. Extracts were counted by LSC. Most of the activity was extracted with ACN (≥70%), with 13% or less in the aqueous phase (total of >83% of the activity was extractable). The pellet was weighed and aliquots taken for combustion/LSC analysis. The radioactivity remaining in the solids was not subjected to further analysis (0.01 to 0.6 ppm of the TRR).

Thin layer chromatography was used to compare extracts ($CHCl_3$:Isopropanol). Acetonitrile extracts from all animals were compared. All profiles, except those of egg whites, were similar within the tissue types, indicating no significant deviations in types of residues between test animals. Egg white profiles where dissimilar, containing from 1 to 3 major components. The differences between egg white profiles was attributed to the variations in residue levels (see table 3). The aqueous extracts from liver and kidney of one of the animals was compared to its ACN extract. Most of the activity remained at the origin, suggesting the presence of more polar components, and was not identified.

For HPLC analysis, radioactivity was extracted from tissue using ACN or MeOH, concentrated and filtered prior to analysis. Three different solvent gradients were used for the various analyses (.05 M ammonium formate in MeOH/H_2O:MeOH). The HPLC analysis indicated the presence of three major components. The components were identified by GC/MS and TLC and HPLC co-chromatography with standards. The components were identified as (A) propiconazole, (B) CGA-118244, and (C) CGA-91305. Kidney ACN extracts were also treated with both beta-glucuronidase, and aryl sulfatase, and the resulting incubation mixtures analyzed by HPLC. Beta-glucuronidase did not result in detectable changes to the HPLC profile. Reaction with aryl sulfatase indicated the presence of conjugates. The results of the HPLC analysis is summarized below.

TABLE 4. CHARACTERIZATION OF ^{14}C-PROPICONAZOLE RESIDUES IN POULTRY TISSUE AND EGGS

Sample (TRR, ppm)	Component %A	%B	%C	Total (ACN only)	% TRR ID' (PPM)
Liver (3.24)	2	4	81	87	62 (2.0)
Kidney (3.33)	2	2	47	51	39 (1.3)
Skin/Fat (0.56)	40	4	43	87	83 (0.47)
Thigh Muscle (0.32)	7	2	80	89	87 (0.28)
Egg White (1.50)	27	51	18	96	94 (1.42)
Egg Yolk (1.74)	15	11	62	88	75 (1.31)

Sample chromatograms from analysis by TLC and HPLC, and mass spectra were submitted.

CBTS Comments/Conclusions, re: Poultry Metabolism Study

The poultry metabolism study is generally acceptable. However, CBTS will withhold its final conclusions on the adequacy of the study until it can be considered in the context of the petitions to which it is relevant (i.e. tolerance petitions on corn and peanuts). Since no poultry feed items are associated with the use on grass seed, the establishment of appropriate tolerances is not contingent upon the adequate delineation of the metabolism of propiconazole in poultry.

We note that no details on sample handling and length of storage were supplied, and no data from storage stability studies on animal commodities were submitted or referenced. This information will be needed to insure sample integrity when considering the relevant petitions.

Analytical Methodology

Methods AG-454A and AG-517 have been validated by the Agency and found adequate for the determination of residues of propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety in crops and livestock commodities (see memo of S. Malak dated 5/28/87). Method AG-454A has been successfully tried on wheat grain, pecan nutmeat, and wheat straw. Method AG-517 has been successfully tried on beef liver, whole milk, and eggs.

Crop samples are extracted by refluxing with 20% concentrated ammonium hydroxide in methanol. Aliquots from the filtered extracts are evaporated to dryness, and the residue are converted to 2,4-dichlorobenzoic acid (DCBA) by heating with an alkaline permanganate solution. Excess permanganate is reacted with sodium meta-bisulfite and the solution is acidified with 6N HCl. After partitioning with 10% diethyl ether/hexane, the organic phase is evaporated to dryness, the DCBA is derivatized with diazomethane. After an additional evaporation step, the residue is dissolved in hexane and cleaned up on an acidic alumina Sep-Pak. The DCBA is quantified on a capillary GLC equipped with an electron capture detector. The methodology for livestock commodities is essentially the same **except** that residues are mechanically extracted from samples using 20% water/acetonitrile. The limit of quantification ranges from 0.02 to 0.2 ppm, depending on the matrix. Both methods have been forwarded to FDA for publication in PAM II (see letter dated 5/28/87 from S. Malak to A. Marcotte). Parent and metabolites have also been tested using FDA Multiresidue methodology. Only the parent can be recovered using the Luke method (see memo of S. Malak dated 4/28/87 and PESTRAK database).

Samples from the ruminant and poultry metabolism studies discussed above were analyzed using Method AG-517. Tissue samples were analyzed in triplicate along with control and propiconazole fortified samples according to procedures described in method AG-517. Fortification levels ranged from .05 to 5 ppm, with recoveries from 74 to 97%. The following table summarizes the results of the validation study.

TABLE 5. SUMMARY OF EXTRACTABILITY, ANALYSIS, AND ACCOUNTABILITY OF ^{14}C TREATED SUBSTRATES BY ANALYTICAL METHOD AG 517

		Extraction		Analysis		GC		
Sample	Tlt. ppm[1]	ppm[2]	%EXT[3]	Final Frac.ppm[4]	Corr.[5]	Final Frac. ppm[6]	Corr.[5]	Account-ability[7]
Poultry Fat Pad	0.72	0.74	103	0.47	0.50	0.57	0.60	83
Poultry Liver	4.98	4.3	87	3.2	3.2	3.7	3.7	75
Poultry Breast Muscle	0.36	0.37	100	0.29	0.30	0.34	0.36	99
Goat Liver	4.52	4.0	88	2.7	2.9	3.0	3.2	70
Goat Fat	0.07	0.065	93	0.037	0.051	0.056	0.078	111
Goat Milk	0.14	0.14	100	.073	.073	.114	.114	81
Goat Leg Muscle	0.08	.078	98	.047	.065	.064	.089	101
Goat Blood	.27	.22	82	.17	.18	.22	.23	84

1. As determined by combustion analysis in metabolism studies.
2. Determined by liquid scintillation counting of aliquots after initial extraction (see method for details). Average of 3 measurements.
3. Average of three extractions divided by total residue (column 3/column 2).
4. Determined by liquid scintillation counting of aliquot of the final fraction (see method for details).
5. Corrected by % recovery from fresh fortifications.
6. Determined by gas chromatography according to AG 517.
7. *Average of column 8 divided by column 2, and multiplied by 100.*

Based on these data, CBTS concludes that adequate enforcement methodology is available. We note that TOX has stated that metabolites containing only the triazole moiety need not be regulated since the levels in plants resulting from the use of propiconazole cannot be distinguished from those which are naturally occurring (see TOX memo of A. Katz dated 5/8/87 and CBTS memo of S. Malak dated 5/14/87).

Residue Data (MRID No.41823305)

Additional residue data were requested in PP No. 9F3706 since the previous data were not geographically representative, did not represent all of the grass species listed on the label, and did not include any data obtained from aerial applications (see 2/7/89 memo of H. Fonouni).

Nine field studies were conducted in Oregon (3), Minnesota (3), Washington (2), and Idaho (1) to determine the magnitude of residues of propiconazole in grasses grown for seed. Plots of bluegrass, bromegrass, timothygrass, fescue and perennial ryegrass were treated using the maximum label rate of four applications of propiconazole at 4 to 8 fl. oz. per application (maximum 4 fl. oz. on bluegrass) in a minimum of 20 gallons of water/A for ground applications or in a minimum of 10 gals water/A for aerial applications. Application intervals ranged from 7 to 14 days. Random samples of grass seed, straw, and screenings were taken 13 to 14 days after the last treatment, and grass forage was taken at the 3 to 6 inch regrowth stage (29 to 289 days after the last treatment). Samples were stored at -20°C until analyzed (maximum 16 months). No storage stability data were submitted in support of this petition or in support of the interim tolerances now established. However, storage stability data on peanut and soybean commodities have previously been reviewed (see PP Nos. 4F3007 and 8F3654). The data indicate no significant degradation of residues for up to 25 months of frozen storage. The petitioner indicates that a storage stability study for weathered residues of propiconazole in grass straw and forage has been initiated and will run through December of 1992.

Residues of propiconazole and metabolites containing the 2,4-dichlorobenzyl moiety were determined using method AG-454B, which is identical to enforcement method AG-454A, except that additional explanation of certain procedural steps was provided. Refer to the above discussion under enforcement methodology for details of procedures. The limit of determination is 0.05 ppm determined as 2,4-dichlorobenzoic acid methyl ester and expressed as propiconazole. Recoveries of propiconazole from samples fortified at levels ranging from 0.1 to 75 ppm ranged from 68 to 105%. Controls contained quantifiable residues in several cases (up to 11 ppm in controls for grass seed screenings. However, due to the magnitude of the residues found in treated samples and the levels

of fortifications used in recovery samples, the petitioner concluded that these levels were insignificant. The following table summarizes the residue data submitted.

TABLE 6. RESIDUES OF PROPICONAZOLE IN GRASS SEEDS, SCREENINGS, STRAW AND FORAGE

Commodity	App. Rate	PHI (days)	Residues, ppm	Average ppm [a]
Seeds	1X	13-14	6.4-36	18 (20)
Seeds[b]	1X	13-14	.37-21	7.2 (8)
Seeds	2X	13-14	.37-93	34 (8)
Straw	1X	13-14	5.3-36	18 (20)
Straw[b]	1X	13-14	1.2-23	11 (6)
Straw	2X	13-14	.27-78	36 (8)
Screenings	1X	13-14	6-67	34 (18)
Screening[b]	1X	14	.89-37	17 (6)
Screenings	2X	13-14	1.5-120	64 (8)
Forage	1X	29-289	<.05-2.4	.55 (20)
Forage[b]	1X	145-279	<.05-1.0	.45 (6)
Forage	2X	30-289	.0`-.80	.81 (5)

a Number in parentheses is number of data points reported
b Data is from aerial application

Sample chromatograms, and details from the conduct of the field trial were submitted.

CBTS Comments and Conclusions, re: Residue Data

CBTS concludes, as did the petitioner, that the residue data do not reflect the label use. The application intervals were significantly shorter than 14 days as specified on the label in many instances (as short as 7 days), and samples of grass seed were taken at less than the 20 day PHI specified (13 to 14 days). CBTS also concludes, contrary to the petitioner's conclusion, that the residue levels of as much as 11 ppm in the control samples is very

significant, and indicate possible misconduct of the study. This further compromises the integrity of these data. The petitioner has indicated that additional field trials are being conducted, and the results of these trials will be submitted at a later date (see S.H. Willett memo of conference dated 2/13/91).

CBTS is unable to recommend for the establishment of new and higher tolerances for these animal feed items because the residue data submitted here are inadequate. Since more data are forthcoming, a determination of appropriate permanent tolerances will be made after these data are reviewed. Although deficient in other ways, these data do suggest however that aerial application is not likely to produce higher residues.

Due to the extenuating circumstances surrounding the need for continued use herbicide in the northwest, we would have no objection to maintaining the interim tolerances of 10 ppm, 5 ppm, and 0.5 ppm on grass seed screenings, hay and forage, respectively until more appropriate data are collected and submitted for review. The interim tolerances were established based on limited data from Minnesota and Oregon where the maximum residues for hay, forage and screenings were 3.32 ppm, 0.27 ppm, and 7.46 ppm, respectively. These data more closely simulated the label use.

We note that no residues over the interim levels have been detected in these feed items since their establishment in 1989 (personal communication with Don Peterson, FDA, Seattle, WA, 206-486-8788).

Secondary Residues in Meat, Milk, Eggs and Poultry

Data from cattle feeding studies were previously reviewed. Lactating cows were fed propiconazole at levels of 15, 75, and 150 ppm for periods of up to 28 days. Milk samples were collected daily and the animals sacrificed at 14, 21 and 28 days during the study period. Samples were analyzed using method AG-359, which determines propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety. This method was found adequate for the purposes of data collection (see 5/14/87 memo of S. Malak). The following residue levels were determined.

	Feeding Levels (ppm)		
	Day 14	Day 21	Day 28
Kidney	0.63	4.7	6.5
Liver	0.81	4.3	5.6
Fat	<.05	.23	.26
Meat	<.05	.11	.18
Milk	<.01	.08	.11

Based on these data, tolerances were established for kidney, liver, meat, fat and milk at 0.2 ppm, 0.2 ppm, 0.1 ppm, 0.1 ppm, and .05 ppm, respectively. The tolerances for kidney and liver were raised to 2.0 ppm as a precaution with the establishment of the interim tolerances on grass seed screenings, hay and forage (see memo of H. Fonouni dated 2/15/89).

A worst case theoretical diet for local beef and dairy cattle could consist of up to 75% fresh grass or grass straw, with the remainder consisting of grain, possibly also treated with propiconazole. Another theoretical diet that may be considered is one consisting of 10% grass hay (straw), 40% grass forage, 30% grass seed screenings, and 20% grain.

CBTS will withhold its final decisions on the adequacy of the tolerances on meat, meat by products and milk until more appropriate residue data are submitted, and appropriate tolerance levels for grass seed screenings, straw and forage can be determined.

Grass seed screenings, hay and forage are not poultry or swine feed items. Therefore, no secondary residues are expected in these livestock commodities as a result of this use on grass grown for seed.

Other Considerations

Anticipated Residues

Propiconazole has been classified as a class C oncogen, and assigned a Q_1^* of 0.079 mg/kg/day. The practice has become to perform dietary exposure estimates using anticipated residues. When tolerances for grass seed screenings, hay and forage were initially proposed in PP No. 9F3706, CBTS (DEB) provided anticipated residue data for propiconazole and its metabolites containing the 2,4-dichlorophenyl moiety in meat, milk, poultry and eggs (see DEB memo of D. Edwards dated 5/23/89). A dietary exposure analysis was subsequently performed using these residue estimates (see SACB/HED memo of J. Tomerlin dated 5/25/89). These estimates used percent crop treated data provided by BEAD. Since nothing has changed as a result of this submission, the DRES analysis would appear to continue to suffice.

The petitioner has submitted additional information which suggests that the tolerances on animal commodities should not be used in estimating human dietary exposure. First and most significant is the fact that grass seed screenings are not a raw agricultural commodity, since screenings are removed from seeds during processing. Treated and untreated screenings are combined, and the screenings are fed to animals in pelletized form. According to the information submitted by the Oregon Department of Agriculture, such

pelleting operations are limited. The ODA has submitted data from the analysis of 21 grass seed screening pellets. Residues ranged from less than .05 to 3.7 ppm (see volume 8 of this submission). A large amount of screenings are also burned. Additionally, grass fields are often burned after seed harvest, suggesting that hay and forage are not important feed items. This information may be considered in estimating exposure when dietary exposure is reevaluated.

The petitioner has also submitted their own percent crop treated data for use in dietary exposure estimates. These data must be reviewed by BEAD prior to use in estimating dietary exposure.

cc: PP Nos. 1F3974, 9F3706, 8F3654, 8F3674, Willett, Circ, PIB/FOD (C. Furlow)
CM2:H7509C:RM803A:X1439:SHWillett:shw-6/3/91
RDI: E. Haeberer, 6/11/91; R. Loranger, 6/11/91

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12101

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Propiconazole - Permanent Tolerances on Grass Used for Livestock Feed or Bedding

TO: Lewis/Stone, PM 21
RD (H7505C)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 4/12/91
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 4/15/91
Section Head, Review Section II
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 4/15/91
Herbicide/Fungicide/Antimicrobial Toxicology Branch
HED (H7509C)

DP Barcode: 163137

Project No. 1-0972

ID#: 1F03974

Tox. Chem. 323EE

Action Requested:

The present temporary tolerances for Propiconazole ("Tilt") on grass used as livestock feed/bedding expire on 6/21/91. The company is proposing permanent tolerances (70 ppm in or on grass seed screenings, 40 ppm in or on grass straw or hay and 2.0 ppm in or on grass forage) that would exeed the present temporary tolerances (10, 5, and 0.5 ppm respectively).

Comments and Recommendations:

1. In a memorandum dated February 1, 1989 (copy attached) it was stated that: "HFASB would have no objections, based on toxicological considerations, to the feeding of treated hay and grass seed screenings with a residue of 10 ppm Propiconazole to livestock, provided that the resulting secondary

residues are within the limits of established tolerances." The information (part of an expedited review request dated February 21, 1991) received with the present action indicates that with a 40 ppm residue level in grass straw (hay), the secondary residues in milk and cattle tissues would still be within established tolerance levels. On this basis then, TOX II would have no objection to the proposed 40 ppm tolerance for this commodity when fed to cattle.

2. This reviewer has spoken (April 12, 1991) with Dr. Gary Orr of Ciba-Geigy regarding the proposed 70 ppm tolerance for grass screenings. According to Dr. Orr, the grass screenings are not fed directly to livestock, but are "processed" first. This processing involves mixing of grass screenings from several areas and, since about 26% of the crop is treated with "Tilt" (because of the expense, treatment with Tilt is done only if necessary), this will "dilute" the residues. It is this reviewer's understanding that the 70 ppm value represents the maximum residue level that would occur in grass screenings from a single area, and that, after processing (including mixing) what would be fed to livestock would have considerably lower residue levels of "Tilt."

3. TOX II defers to DEB as to whether the rationales presented by the registrant are acceptable, and as to whether calculations of residue levels in milk and cattle tissues are also applicable to goats, hogs, horses and sheep. TOX II can accept the proposed tolerances provided the secondary residues in milk and meat are within established tolerances.

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
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EPA SERIES 361

APR 12 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Request for an Expedited Review: Propiconazole, Increased Tolerances from Use of Tilt on Grasses Grown for Seed

From: Elizabeth T. Haeberer, Chemist
Chemistry Branch - Tolerance Support
Health Effects Division (H7509C)

Elizabeth T. Haeberer

Thru: Richard D. Schmitt, Ph.D., Chief
Chemistry Branch - Tolerance Support
Health Effects Division (H7509C)

R. Loranger for RDS

To: Anne E. Lindsay, Director
Registration Division (H7505C)

Registration Division has requested an expedited review for propiconazole on grasses grown for seed. As per our telephone communication of April 12, 1991 (Elizabeth Haeberer, CBTS and Carl Grable, RD), it will not be possible to complete the review of these data packages by May 14, 1991. The primary reviewer for this chemical, Stephanie Willett, is currently reviewing an **expedited** action for avermectin on tomatoes, which is due April 24, 1991.

Since the reviewer will not be able to address the propiconazole data until the end of April, and due to the complexity of the data submission to be reviewed for propiconazole on grasses grown for seed, CBTS proposes a deadline of June 7, 1991 for completion of the subject review. Please advise CBTS as to the acceptability of this revised due date.

cc: P. Fenner-Crisp, R. Schmitt, S. Willett, E. Haeberer

13544

R062889

Chemical:	**Propiconazole**
PC Code:	**122101**
HED File Code	**11500 Petition Files Chemistry**
Memo Date:	**08/06/2003 12:00:00 AM**
File ID:	**DPD178453; DPD192904; DPD191344; DPD194138; DPD191329; DPD187417; DPD190266; DPD185251; DPD176899; DPD176958; DPD177496; DPD162311; DPD163137**
Accession Number:	**412-04-0144**

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