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L. Rossi

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

FEB 7 1989

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EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 9F3706 and 1/6/89 Amendment to the Petition
Tilt^R (Propiconazole) in or on Hay, Forage, and Seed
Screenings of Grasses Grown-for-Seeds. Evaluation of
Analytical Methodology and Residue Data.

MRID No(s): 408907-01
DEB No(s): 4700, 4824

FROM: H. Fonouni, Ph.D., Chemist *H. E. Fonouni*
Dietary Exposure Branch
Health Effects Division (TS-769)

THRU: Richard D. Schmitt, Acting Chief *Richard D. Schmitt*
Dietary Exposure Branch
Health Effects Division (TS-769)

TO: L. Rossi, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767)

and

Fungicide-Herbicide Support
Toxicology Branch
Health Effects Division (TS-769)

This review has been expedited as requested by Ann Lindsay, Registration Division (refer to memorandum of 1/23/1989 by H. Fonouni; Review of Data Submitted by the Oregon Department of Agriculture on residues of Tilt^R in or on Grass Seed Screenings).

The petitioner, Ciba-Geigy Corporation proposes establishment of group tolerances for the residues of the fungicide 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 compound in or on the following agricultural commodities (proposed tolerances in ppm are given in parenthesis):

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Section 40 CFR 180.434 -
Hay, Grasses Grown for Seed
Forage

(5.0)
(0.5)

In addition, an interim tolerance of 10.0 ppm (expiration date 12/31/1990) has been proposed in an amendment (1/6/89) to the subject petition for grass seed screenings.

Permanent tolerances, in ppm, currently established according to 40 CFR 180.434 include pecan, and barley, rice, rye, and wheat grain (0.1 each), bananas (0.2), meat and fat (0.1, each), liver and kidney (0.2, each), meat by products (except liver and kidney, 0.1), milk (0.05), and eggs (0.1). Established tolerances in or on animal feeds include barley, rye and wheat straw (1.5 ppm, each), and rice straw (3.0 ppm). Currently pending tolerances, expressed in ppm, for other agricultural commodities include celery (5.0), corn forage and fodder (10.0, each), corn grain (0.1), pineapples and pineapple fodder (0.1), legume vegetables (0.5), legume vegetable foliage (5.0), peanuts (0.2), peanut hulls (1.0), and peanut hay (20.0).

CONCLUSIONS

1. Adequate information has been provided on the nature and composition of the fungicide.
2. Since grasses may be harvested for seeds on ranges, the label should be revised such that the rangeland application of the fungicide is prohibited. In addition, either aerial application of the Tilt^R should be prohibited or appropriate field residue data in support of the latter application technique should be provided.
- 3a. The nature of the residues in plants is adequately delineated. The residues of concern are the parent fungicide 1-([2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl)-1H-1,2,4-triazole and its metabolites which are determined as 2,4-dichlorobenzoic acid.
- 3b. Although the previously submitted metabolism data were found to be adequate in conjunction with previous petitions which led to a negligible dietary exposure of livestock to residues of the fungicide and its metabolites, the current use would result in significantly higher dietary burden. The petitioner should, therefore, conduct the requested metabolism study in lactating cows or goats using phenyl labelled ¹⁴C-CGA-64250 to determine the nature of metabolites present, and provide an adequate material balance; the metabolism study was initially

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requested in conjunction with petitions on agricultural commodities, peanut (pp# 8F3654) and corn (pp# 8F3674).

4a. Analytical methodologies provided are adequate for determination of known residues of 1-([2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl)-1H-1,2,4-triazole and its metabolites in the subject commodities. However, recovery data need to be submitted for grass forage.

4b. For the purpose of establishing permanent tolerances on the subject feeds, DEB can not presently address the adequacy of previously submitted methodology for livestock products, until the result from the study requested in aforementioned conclusion 3b is evaluated. Should the livestock metabolism study lead to the detection of any new metabolite(s) of toxicological concern, additional enforcement method(s) may be required.

5a. Additional residue data reflecting appropriate geographic representation as well as representative grass species should be provided on the subject feeds; refer to the section on Magnitude of the Residues. In addition, storage stability data should be provided on hay.

5b. Although residue data on livestock products have been provided in conjunction with other petitions, until the result from the requested metabolism study, 3b, is evaluated, DEB can not comment on the adequacy of available data.

6a. The petitioner has proposed group tolerances of 0.5 and 5.0 ppm for residues of 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 in or on hay and forage (regrowth), respectively, of grasses grown-for-seeds. In addition, an interim tolerance of 10.0 ppm has been proposed for seed screenings. DEB can not presently comment on the adequacy of the proposed permanent tolerances, until the deficiencies raised in aforementioned conclusion 5a are resolved. TOX considerations permitting, however, DEB would not object to establishing tolerances with expiration dates on the subject feeds.

6b. For the purpose of establishing permanent tolerances on the subject feed items, DEB can not presently address the adequacy of established tolerances on meat, fat, liver, kidney, meat by products, and milk until the issue raised in conclusion 3b is resolved.

7. An International Residue Limit Status form is included in the review. Since there is no Codex step 6 or above on the subject commodities, the compatibility issue is not relevant to the proposed tolerances. However, it should be noted that, the

Agency's approach for determination of residues of propiconazole differs from that of Codex. While residues are determined and expressed as propiconazole by FAO/WHO, the Agency determines the combined residues of 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole and its metabolites containing 2,4-dichlorobenzoic acid and, expresses the residues as the parent fungicide.

RECOMMENDATIONS

As a result of aforementioned conclusions; 2, 3b, 4a, 4b, 5a, 5b, 6a, and 6b; DEB recommends against establishing the proposed permanent tolerances on the subject commodities. TOX considerations permitting, however, DEB would not object to establishing tolerances with the proposed expiration date on the subject feeds, forage, hay, and seed screenings. It should be noted that, currently, the Agency considers application of pesticides to grasses grown-for-seed as a food use thereby requiring establishment of tolerances, according to the section 408 of the FFDCA and 40 CFR 180.3, for the appropriate feed items derived from the subject agricultural commodity. When Tilt^R was initially registered, however, this use pattern was considered a non-food use.

NOTE TO PM

DEB recommends that a copy of this review be forwarded to the petitioner. In addition, given the feed use of the subject commodities and impracticality of labeling restrictions pertaining to this use, DEB reiterates its previous recommendation (memorandum of 1/23/1989; Review of Data Submitted by the Oregon Department of Agriculture on residues of Tilt^R in or on Grass Seed Screenings, by H. Fonouni) on a need for establishing tolerances on grass hay and seed screenings of grasses grown-for-seed. Further, in the absence of appropriate labeling restriction prohibiting the feed use of forage, a tolerance should also be established on the corresponding forage.

DETAILED CONSIDERATIONS

Manufacture and Formulation

Adequate information has been provided on this topic in conjunction with pp# 1G2530 and pp# 4F3007 (memorandums of 1/7/1982 and 5/15/1984 by J. Worthington and A. Smith, respectively). Recently, additional information was reportedly provided on a proposed modification in the manufacturing process (MRID Nos. 405837-01 to 405837-03). However, review of this information is currently under the purview of the Registration

(5)

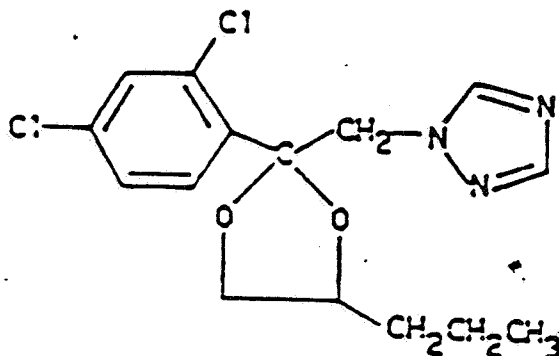
Division. The formulated product, Tilt^R 3.6E, containing 3.6 lbs ai/gallon is produced from [REDACTED]. The impurities present are not expected to result in a residue problem. The formulation has a composition of 41.8% active and 58.2% inert ingredients. The inert ingredients in the product have been cleared under Section 40 CFR 180.1001.

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

Company Codes for the Active Ingredient: CGA-64250

Common Name: Propiconazole (Pending ISO)

Structural Formula:



Proposed Use

Tilt^R fungicide is to be used, for control of rusts (puccinia spp.), powdery mildew, and selenophoma stem eyespot, on perennial ryegrass, fescues, bluegrass, orchardgrass, and wheatgrasses grown-for-seed in NE, OR, WA, ID, and Minnesota. The fungicide, 4-8 fl oz (5-10 g ai)/A, in 10 and 20 gallons of water is to be used for aerial and ground applications, respectively. Tilt is to be applied, on the appearance of selenophoma infections and rust pustules, in the late spring or early summer. The applications are to continue at 14-21 day intervals as needed to maintain rust control until the maturity of seeds. A maximum of 32 fl oz of Tilt (4 X 100 g ai)/A/season may be used with the last application being made 20 days prior to the harvest. Restrictions on the label include feeding hay to livestock and grazing of livestock on the treated areas within 20 and 140 days of the last application, respectively.

INFORMATION WHICH MAY REVEAL A MANUFACTURING PROCESS IS NOT INCLUDED

Comments:

Since grasses may be harvested for seeds on ranges, the label should be revised such that the rangeland application of the fungicide is prohibited. In addition, either aerial application of the Tilt^R should be prohibited or appropriate field residue data in support of the latter application technique should be provided; refer also to the section on the Magnitude of the Residues.

Nature of The Residues

I. Plants

The metabolism of CGA-64250 has been studied in wheat, peanuts, and grapes (pp# 4F3007, memorandum of 5/15/1984 by A. Smith). A myriad of metabolites resulting from beta-oxidation of n-propyl side chain, reductive deketalization of dioxolane ring, and cleavage of the alkyl bridge between phenyl and triazole ring systems have been reported (Figure 1).

Comments:

For the purpose of this petition, DEB considers the nature of residues in the subject commodities adequately understood.

II. Animals

The metabolism of CGA-64250 in lactating goats and rats has been reported (pp# 4F3007, memorandum of 5/15/1984 by A. Smith). The major metabolites, analogous to the plant metabolism, arise from oxidation of the alkyl side chain, dioxolane ring opening, and cleavage of the alkyl bridge between the phenyl and triazole ring systems. A scheme representing the metabolism of CGA-64250 in goats is provided in Figure 2.

Comments:

On evaluation of the information/data provided on metabolism of the fungicide in lactating goats, it was noted that the petitioner has accounted for less than 21% of the residues of potential toxicological concern in livestock commodities (tissue, milk) using triazole labelled ¹⁴C-CGA-64250 as well as phenyl and triazole labelled ¹⁴C-CGA-64251. The latter product is a homolog of the former containing an ethyl side chain instead of a propyl group (EPA Accession No. 072214). Although the submitted data were found to be adequate in conjunction with previous petitions

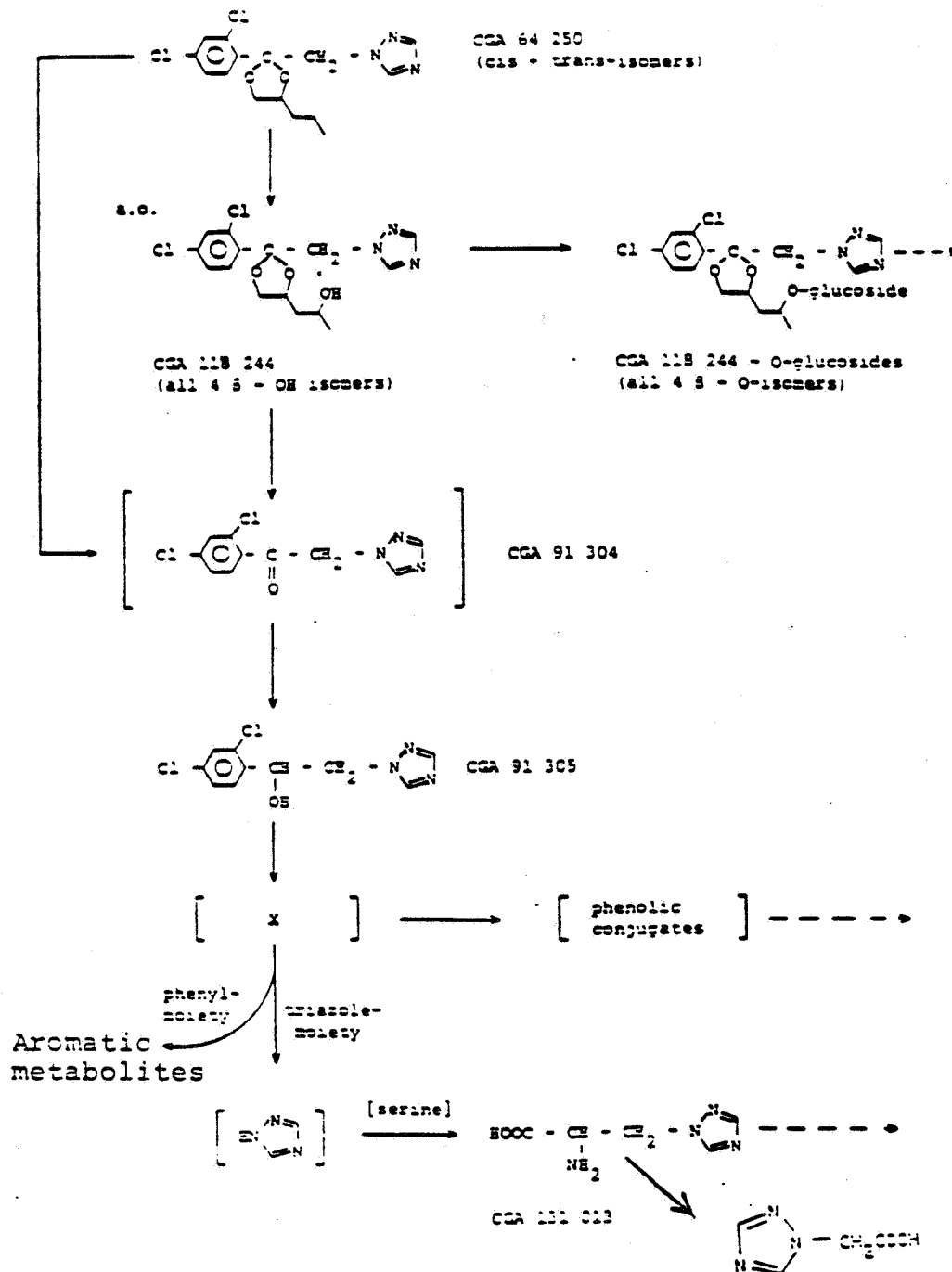


FIGURE 1. PROPOSED PATHWAYS FOR THE METABOLISM OF CGA-64250 IN PLANTS INCLUDING PECANS

(Reproduced from pp# 4F3007)

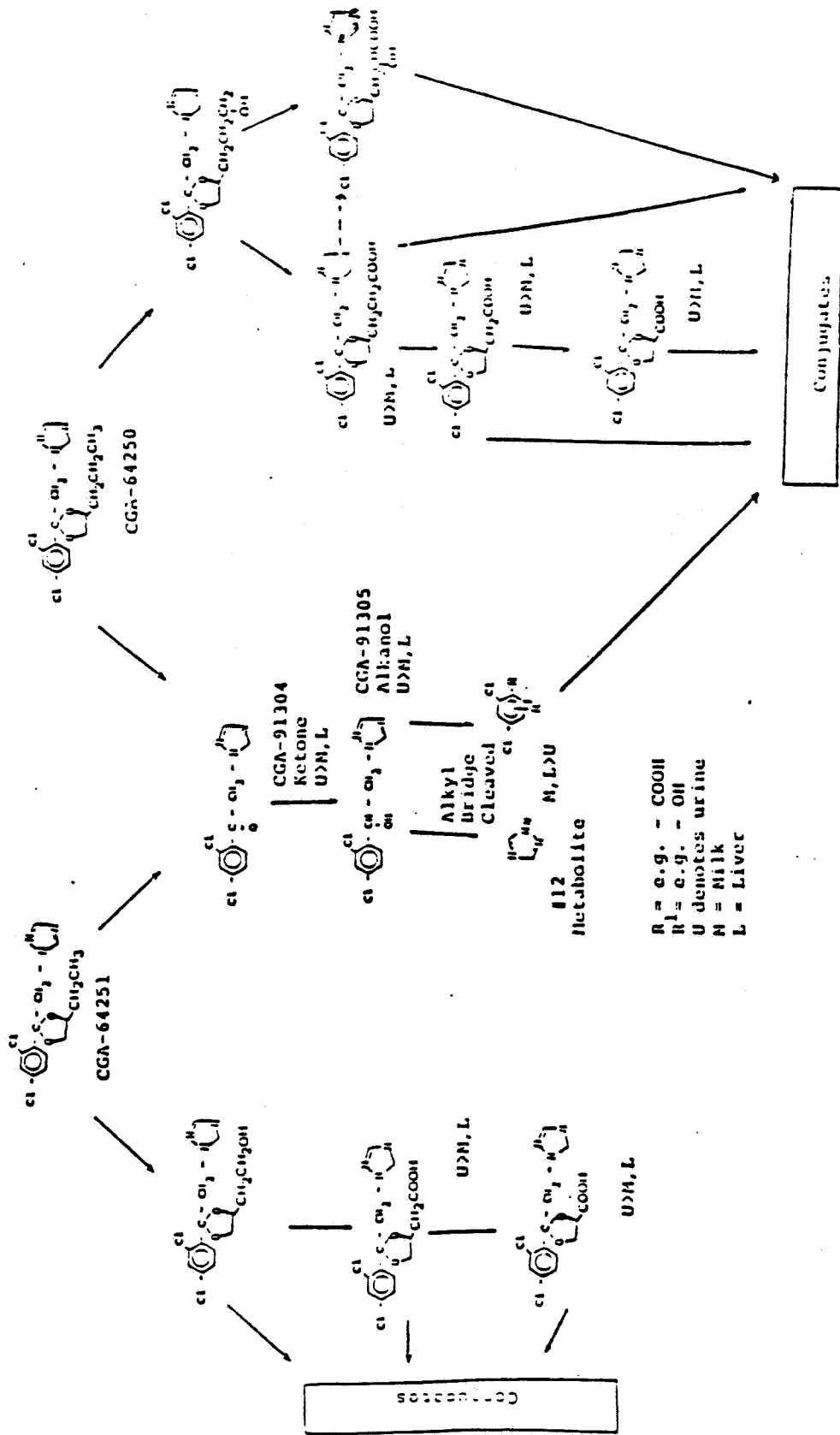


FIGURE 2. PROPOSED METABOLIC PATHWAYS OF CGA-64250 AND CGA-64251 IN GOAT

ABR-83062

(Reproduced from pp# 4F3007)

which led to negligible dietary intake (<1 ppm) by livestock, the current petition is expected to result in a maximum dietary burden of about 6 ppm in cattle. This value, reflecting a worse-case exposure, was calculated based on the proposed tolerances for grass hay, and screenings and the contribution of the subject feeds to the diet (upto 70 % hay; Table II, Pesticide Assessment Guidelines, Subdivision O, and 25% seed screenings; memorandum of 11/30/88 by the Oregon Department of Agriculture). For the purpose of permanent tolerances the petitioner should, therefore, conduct a metabolism study in lactating cows or goats using phenyl labelled ¹⁴C-CGA-64250 to determine the nature of metabolites present, and provide an adequate material balance. A revision of tolerance expression might be required, if new metabolites of toxicological concern are detected in animal commodities.

Analytical Methodologies

I. Plants

The method provided, AG-415, is similar to method AG-454A which was submitted in conjunction with other petitions (pp# 4F3007, 4F3074, 4E3026; memorandum of 5/28/1987 by S. Malak). The latter method has undergone successful method trial by the Agency and is to be sent to FDA for publication in PAM II. Method AG-415 differs, primarily, from the enforcement method in the oxidation step which converts the parent fungicide and its metabolites containing the 2,4-dichlorophenyl moiety to 2,4-dichlorobenzoic acid. While a 16-hour reflux with 12N nitric acid is used in method AG-415, the enforcement method utilizes a 1-hour refluxing period with basic potassium permanganate; refer to the memorandum of 11/22/88 (pp# 8F3654).

Limit of Detection: 0.5 picograms (0.05 ppm).

Chromatograms:

Representative chromatograms have been provided for the standards, untreated controls, fortified, and treated samples of various commodities.

Recoveries:

The average recoveries for untreated samples of grass hay and seed fortified with CGA-64250 are presented in Table I.

Table I. Average Recoveries For CGA-64250

<u>Grass Commodity</u>	<u>Average Recoveries¹</u>
Hay	86 ± 9
Seeds	91 ± 15

1. Average percent recoveries were obtained for fortifications of 0.01-0.07, and 0.01-0.10 ppm for grass hay and seeds, respectively.

Comments:

The petitioner should provide recovery data for grass forage.

II. Animals

Although analytical methodology has been provided in conjunction with other petitions (pp# 4F3007, 4F3074, 4E3026; memorandum of 5/28/1987 by S. Malak), DEB can not presently address the adequacy of previously submitted methodology for livestock products until result from the study requested, Nature of the Residues, is evaluated. Should the new metabolism study lead to the detection of any new metabolite(s) of toxicological concern, additional enforcement method(s) may be required.

Magnitude Of The Residues

I. Plants

Sample History:

Field studies were conducted in Oregon and Minnesota using a variety of grasses. Foliar applications were made using ground application techniques. The fungicide Tilt^R 3.6E was generally applied at a rate of 100 g ai/A (1X), a maximum of four applications were made. Samples of grass hay and seed were taken during the harvest (20-36 days following the last application), and those of forage at the regrowth stage (141-149 days following the last application). The collected samples were not trimmed or washed. Removal of surface dirt was accomplished by shaking the commodities. The samples were frozen and shipped in dry ice to the petitioner, and then kept at -15 degrees C for about 7 months prior to analysis.

Storage Stability:

The Petitioner cites the storage stability data provided in conjunction with previous petitions (pp# 4F3007 and 8F3654, EPA Accession No. 072215). The data indicate a lack of significant

dissipation of the residues in soybean seed/fodder and peanut fodder/shells for a period of 25 and 6 months, respectively.

Comments:

1. Storage stability data should be provided for hay or another suitable dry commodity (for example, straw).

Residue Data:

A summary of residue data provided on grass hay, forage (regrowth) and seed screenings appears in Table II. In addition, the corresponding residues of propiconazole/metabolites in grass seeds are reportedly 0.89-6.4 ppm (average = 2.25 ppm, N = 10; PHI = 20-30 days). Further, monitoring residue data have been provided on grass seed screenings by the Oregon Department of Agriculture and requested by Ciba-Geigy to be used as part of an amendment to the subject petition. The residues of propiconazole/metabolites found in/on seed screenings and screening pellets (the latter is either composed solely of seed screenings or seed screenings as a component of various pelletized feeds) were, respectively, 0.5-4.2 and below the detection limit to 5.8 ppm. It should be noted that, the previously reported value of 20 ppm (actually 18 ppm) by FDA (89-OR-01, memorandum of 12/16/1988 by L. Propst) has not been reproducible according to FDA; this value obtained in the preliminary studies may have been the result of unexplainable anomalies encountered in the instruments and the methods used (correspondence of 1/10/1989 by D. Peterson, FDA Pacific Region).

Comments:

1. The fungicide is currently registered for ground and aerial applications. However, no residue data have been provided in support of the proposed tolerances using the latter application technique. The petitioner should either revise the label restricting the aerial application or provide the appropriate residue data; refer also to the section on Proposed Use.
2. Considering the expected statistical variability of the field residue data, residues of CGA-64250 and its metabolites do not vary significantly with grass species (bluegrass, ryegrass, and fescue) and preharvest intervals for hay. The maximum and average residues (shown in parenthesis) of propiconazole/metabolites, expressed in ppm, were 3.32 (2.05, N = 10) for PHI of 20-30 days in Oregon. In Minnesota with application rates lower than the maximum permitted by the label (3 X 100 instead of 4 X 100 g ai/A) and using only two representative grass species, ryegrass and bluegrass (instead of the three representative

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Table II. Residues of Propiconazole/Metabolites in Grass Hay, Forage, and Seed Screenings of Grasses Grown for Seeds.¹

PHI (Days)	Grass Hay		Grass Forage		Seed Screenings	
	Range	Average	Range	Average	Range	Average
20	2.10-2.91	2.5				
22	2.2	2.2				
24	0.73-1.05	0.79				
28	2.70-3.32	3.0			6.86-7.46	7.16
30	1.2	1.2				
20-30	0.89-3.32	2.0 (N=10)				
141			0.11-0.12	0.12		
145			0.27	0.27		
141-145			0.11-0.27	0.17 (N=3)		

1. The residues are expressed in ppm; the data were obtained from grasses (bluegrass, ryegrass, and fescue) treated with 4 X 100 g ai/A (1X = 100 g ai/A) in Oregon which constitutes about 90% of the total production in the Pacific Northwest. Data have also been provided from Minnesota using application rates lower than the maximum permitted rate. The residues reported for ryegrass and bluegrass as a result of an application rate of 3 X 100 g ai/A were 0.08-1.68 (PHI = 22-36) and 0.14 ppm (PHI = 149) for grass hay and forage, respectively. The values presented have not been corrected for controls which were generally below <0.05 ppm.

species required according to 40 CFR 180.34 f 9 xvii), the residues ranged from 0.08 to 1.68 ppm with PHI of 22-36 days. Additional field residue data should be provided on bromegrass or a major Midwestern grass species.

3. The limited field residue data provided from Oregon indicate maximum and average residues, in ppm, of 0.27 (average = 0.17, N = 3), PHI of 141-145 days, and 7.46 (average = 7.16, N = 2), PHI of 28 days, in/on grass forage and seed screenings/chaff, respectively. The corresponding value for forage obtained from field studies conducted in Minnesota, using the lower application rate (3 X 100 g ai/A/season), is 0.14 ppm (PHI = 149 days). Additional residue data reflecting appropriate geographic representation as well as grass species are required for forage and seed screenings. Such data should be generated from grasses treated with maximum permitted application rate. It should be noted that, the enforcement data provided by the Oregon Department of Agriculture on seed screenings can not be employed for establishing a permanent tolerance on the subject commodity, since information such as a pesticide application rate, sample history, and sample composition (the proportion of treated versus untreated agricultural commodities) are necessary for evaluation of the residue data. These data in conjunction with other information/data may, however, be considered by the Registration Division for establishing a tolerance with an expiration date on the feed item.

II. Animals

Although residue data have been provided on residues of CGA-64250 and its metabolites in livestock commodities in conjunction with previous petitions (pp# 4F3074, memorandum of 7/12/1984 by A. Smith ; pp# 4F3007, 4F3074, and 4E3026 memorandum of 5/14/1987 by S. Malak), until the result from the metabolism study, Nature of the Residues, is evaluated DEB can not comment on the adequacy of available data.

Other Considerations - Proposed Tolerances

I. Plant Commodities

The petitioner has proposed group tolerances of 0.5 and 5.0 ppm for residues of 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 in or on hay and forage (regrowth), respectively, of grasses grown-for-seeds. In addition, an interim tolerance of 10.0 ppm has been proposed for seed screenings. DEB can not presently comment on the adequacy of the proposed permanent tolerances, until the deficiencies raised in the section on Magnitude of the Residues are

satisfactorily addressed. TOX considerations permitting, however, DEB would not object to establishing tolerances with expiration dates on the subject feeds.

II. Livestock Commodities

The established tolerances, expressed in ppm, for meat/fat, liver/kidney, meat by products (except liver and kidney), and milk are 0.1, 0.2, 0.1, and 0.05, respectively. For the purpose of establishing permanent tolerances on the subject agricultural commodities, DEB can make no conclusion as to the adequacy of existing tolerances on livestock commodities until the deficiency raised, Nature Of The Residues, is resolved. Should the metabolism study lead to the detection of any new metabolite(s) of toxicological significance, additional residue data and enforcement methodology may be required.

cc: Reading File, Circulation, Reviewer (H. Fonouni), pp# 9F3706, ISB/PMSD (E. Eldredge).

TS - 769:DEB:Reviewer(HF):CM#2,Rm803:557-7561:typist(hf): 1/31/1989.

RDI:Section Head:JHOnley:11/18/1988:Deputy Chief:RDSchmitt: 2/1/1989.

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL TILT R, Propiconazole

J. Jones
2/1/89

CODEX NO. 160

CODEX STATUS:

No Codex Proposal
Step 6 or above (for given
commodities)

Residue (if Step 8):
Propiconazole

PROPOSED U.S. TOLERANCES:

Petition No. 943706

RCB Reviewer H. Forouhi

Residue: propiconazole and
its metabolites determined
as 2,4-dichlorobenzoic acid

Crop(s) Limit
 (mg/kg)

Crop(s) Limit
 (mg/kg)

forage (regrowth) 0.5

hay 5.0

seed screenings 10.0
(of grasses grown for
seed only)

CANADIAN LIMITS:

No Canadian limit
Residue: _____

MEXICAN LIMITS:

No Mexican limit
Residue: _____

Crop(s) Limit
 (mg/kg)

Crop(s) Limit
 (mg/kg)

NOTES:

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