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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAY 14 1987

MEMORANDUM

SUBJECT: PP#'s 4F3074, 4F3007, and 4E3026. Propiconazole (Tilt® or CGA-64250) on Crops and Livestock Commodities. Residue Data in or on Livestock Commodities Using Ciba-Geigy's Method AG-359. Amendment of April 2, 1987. MIRD No. 401507-01. RCB No. 2172.

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

TO: Lois Rossi, PM #21
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and

Toxicology Branch
Hazard Evaluation Division

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

Note: This is an expedited review at the request of the Registration Division's Director, Mr. E. F. Tinsworth (Letter of 4/14/87).

Introduction and Background

In response to RCB memo of subject petitions (S. Malak and W. T. Chin, 3/20/87), Ciba-Geigy submitted residue data for propiconazole (Tilt® or CGA-64250) in or on livestock commodities using Ciba-Geigy's Analytical Method AG-359.

The available residue data, previously submitted in connection with subject petitions, were generated mainly with Ciba-Geigy's Method AG-356 for plant commodities and AG-359 for livestock commodities. Both methods,

however, failed method trials because of lengthy procedures, unavailability of state of the art instrumentation, and for poor resolution (PP#4F3007, memo of R. F. Thomas, 9/9/86).

Upon re-evaluation of the residue data and methods involved, RCB reached the following conclusions (Malak/Chin memo of 3/20/87):

- 1(a). Because of the poor resolution of method No. AG-359 used to determine propiconazole residues in animal commodities, all the residue data of animal commodities generated from this method are considered invalid. Accordingly, the petitioner should be advised to submit adequate residue data in support of the proposed tolerances for residues of propiconazole in/on animal commodities. If the petitioner has reserved samples which can be proved to be adequate by storage stability data, analyses of the reserved samples with adequate methodology will be acceptable.
- 1(b). The above requirement does not affect tolerances as requested in PP#4F3007 (pecan) and PP#4F3026 (banana) because no animal commodities are involved in these petitions.
2. For method No. AG-356, however, the resolution of the GC/MS analyses is reasonably adequate. Therefore, all the residue data of plant commodities generated from method AG-356 are considered valid.
3. All future residue data should be generated with adequate methodology.

Currently, RCB is evaluating and reporting on the results of two method trials for Tilt, Method AG-454A for crops and AG-517 for livestock, recently completed by the Analytical Chemistry Laboratory/COB/BUD in Beltsville (memo of Everette Greer, et al, 4/27/87). These two methods are said to be an updated versions of the analytical methods previously submitted in connection with subject petitions for crops and livestock commodities. Neither Method AG-454A nor AG-517 is capable of determining compounds containing only the triazole moiety (without the 2,4-dichlorophenyl group) contributed by propiconazole. There is, however, a method specific for such a determination as triazolealanine.

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]-1-H-1,2,4-triazole, in/on the grains 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; kidney and liver of cattle, hogs, horses, sheep, and poultry at 0.1 ppm (PP#4F3074); pecans at 0.1 ppm (PP#4F3007); and bananas at 0.2 ppm (PP#4E3026). The chemical is regulated under 40CFR§180.434.

In this submission, the study title for livestock residue data is "Response to EPA's Concern Regarding the Validity of Analytical Method AG-359 to Determine Propiconazole Residues in Animal Commodities (Magnitude of Residues)." The study is authored by M. W. Cheung of Ciba-Geigy, dated April 1, 1987 and is contained in three volumes 624 pages in length. The tests are identified as Ciba-Geigy's No. ABR-87039, were conducted by the Agricultural Division of Ciba-Geigy in Greensboro, North Carolina.

The petitioner submitted the raw data from animal feeding studies containing the residue data and chromatograms; a summary of this data was previously submitted and reviewed in connection with PP#4F3074 (memo of A. Smith, 7/12/84). In addition, some residue data and chromatograms are included where livestock samples were reanalyzed using the updated analytical method, AG-517. The latter set of data were presented in a table comparing the results of AG-517 against previously generated data using method AG-359.

A. Residue Data Generated Using Method AG-359

Since the data presented are from the animal feeding studies, it is appropriate to briefly describe these studies (see PP#4F3074).

Livestock Feeding Study

Lactating cows were fed propiconazole in the daily diet at levels of 15, 75, and 150 ppm for periods up through 28 days. Milk samples were collected daily and the animals were sacrificed at 14, 21 and 28 days during the study period. Sample analysis of milk and tissue were performed using method AG-359. The method determines total propiconazole and metabolites containing the 2,4-dichlorophenyl moiety. Residues are expressed as propiconazole-equivalent. Method sensitivity was reported at 0.01 ppm for milk, 0.1 ppm for the kidney and 0.05 ppm for other tissue.

Poultry Feeding Study

Laying hens were fed propiconazole in their daily ration at levels of 7.5, 37.5, and 75 ppm for 28 days. Egg samples were collected daily and chickens were sacrificed at weekly interval and were analyzed using analytical method AG-359. The method determines total

residues of propiconazole as the methyl ester of 2,4-dichlorobenzoic acid and reported as propiconazole-equivalent.

Residue Data

In this submission, raw residue data and chromatograms were indexed in 39 sections for easy access. Table 1 presents a summary of the residue data for livestock tissue at various feeding levels and interval in days from feeding.

Since milk and egg samples were collected daily and analyzed at various intervals, a summary of propiconazole residues in these two commodities is to follow Table 1.

Table 1. Maximum propiconazole Residues in Animal Tissues at Various Feeding Levels and Interval Using Analytical Method AG-359

1. Cattle

Commodity	Interval From Feeding (Days)								
	14			21			28		
	Feeding Level (ppm)								
	15	75	150	15	75	150	15	75	150
Meats	<0.05	0.11	0.18	<0.05	0.08	0.13	<0.05	0.05	0.11
Kidney	0.61	3.04	6.48	0.56	4.68	5.0	0.63	3.68	5.5
Liver	0.5	4.0	4.6	0.81	4.3	5.3	0.57	2.7	5.6
Fat	<0.05	0.23	0.26	<0.05	0.15	0.19	<0.05	0.08	0.17

2. Poultry

	Feeding Level (ppm)								
	7.5	37.5	75	7.5	37.5	75	7.5	37.5	75
Meats	<0.05	----	----	<0.05	<0.05	0.07	<0.05	<0.05	0.06
Liver	<0.1	0.1	0.47	-----	0.08	0.39	<0.1	0.16	0.3
Fat	-----	<0.05	0.11	-----	<0.05	0.06	-----	<0.05	0.05

Milk: No detectable residues at the 15 ppm feeding level (<0.01 ppm). A maximum of 0.1 ppm and 0.11 ppm residues were detected at the 75 and 150 ppm feeding levels, respectively.

Eggs: No detectable residues at the 7.5 ppm feeding level (<0.05 ppm). At the 37.5 ppm feeding level residues of 0.13 ppm were detectable on the 3rd day of feeding and reached a maximum of 0.18 ppm on the 14th day of feeding. Residues on 28 day were 0.06 ppm. At the 75 ppm feeding level, residues appeared on day 3 at 0.06 ppm and reached a maximum of 0.37 ppm on day 21 and were 0.22 ppm on day 28.

Sample chromatograms of control, fortified, and treated samples for each commodity are included. In general, the chromatograms are characterized by interfering peaks at or about the same retention time as the peak of interest, 2,4-dichlorobenzoic acid. The peak of interest can easily be overlooked. Further, the base line noise makes it difficult to construct a base line for quantitation. For these reasons, method AG-359 failed the MTO and can not be recommended for as the method of enforcement. The method, however, may be used to collect residue data by experienced personnel familiar with the technique. For this reason, we are reviewing the raw data for clarity, reproducibility, and interpretation by the registrant.

This submission presents the raw data and chromatograms demonstrating acceptable resolution and reproducibility for various livestock commodities. Recoveries at the limit of detection were visible and residues above limit of detection were measurable. Furthermore, Ciba-Geigy reported that all residue values were corrected for recovery. Also, a correction was made where a peak was visible in a control sample at the same retention time as the peak of interest (2,4-dichlorobenzoic acid). They also reported that in situations where peak resolution was questionable due to either late elution or to interference, the samples were reanalyzed using additional cleanup or improved GC conditions until a satisfactory chromatogram was obtained.

The deficiency cited in RCB memo of subject petitions (Malak/Chin, 3/20/87) is resolved.

B. Residue Data Generated Using Method AG-517 vs. Method AG-359

In this submission, some livestock data were presented where comparison can be made between the residue data previously generated using Method AG-359 and the new enforcement methodology, AG-517. It should be noted, however, that sample analysis using Method AG-517 was

conducted in January, 1987; whereas, previously analyzed samples using Method AG-359 was conducted in June and July of 1981. For this reason, a meaningful assessment on the data presented may be difficult since samples were stored for a period of 6 years prior to analysis using Method AG-517 where chemical transformation of propiconazole during prolonged periods in frozen conditions are unknown.

A storage stability study is discussed in connection with PP#4F3007 (memo of A. Smith, 5/15/84) which demonstrated that propiconazole is stable under frozen conditions for periods of up to 25 months. Nevertheless, the data are presented in Table 2.

Table 2. Propiconazole Residues in Selected Animal Samples Determined at Various Interval From Feeding Using Analytical Methods AG-359 and AG-517.

Sample	Residues (ppm) at Various Interval (Days)					
	14		21		28	
	Analytical Method AG-					
	359	517	359	517	359	517
Meats	0.18	0.17	0.13	0.1	0.11	0.1
Fat	0.26	0.42 0.59	0.19	0.19 0.21	0.17	0.2 0.29
Liver	4.6	8.9 8.4	5.3	7.4 6.4	5.6	5.0 5.0
Milk	----	0.14 0.09	0.08	0.11 0.07	0.1	0.14 0.1
Eggs	0.18	0.57	----	----	0.36	0.5

It can be seen from Table 2 that inspite of the prolonged period of storage in frozen conditions, the enforcement methodology, AG-517, determined higher residues, particularly in the liver, almost twice as much as that determined by method AG-359 at the lower preslaughter intervals of 14 and 21 days).

Controls for liver were reported as 0.16 ppm and 0.08 ppm. Because of this background of the proposed enforcement method we recommend that the liver and kidney tolerances be established at 0.2 ppm (see below for our recommendations for the remaining livestock commodities).

For these reasons, it is our judgment that residue data in livestock commodities using method AG-359 and the enforcement methodology, AG-517, are relatively comparable with method AG-517 perhaps measuring more residues containing the 2,4,-dichlorobenzoic acid.

RCB Comments and Responses to Previous Deficiencies in PP#4F3074:

RCB has previously concluded that no food or feed additive tolerances are needed for propiconazole since no residues (<0.05 ppm) were detectable in the raw agricultural commodity, the grains of barley, rice, rye, and wheat. As a result, no concentration of residues is likely to occur in the processing fractions. This conclusion, however, is contingent upon imposition of the following label revision stated in Conclusion #1, PP#4F3074, memo of A. Smith, 4/9/85): "A label revision is needed which states that no application is to occur after flag-leaf emergence (instead of before boot split and head emergence)."

Further, the petitioner needs to address deficiencies #4(a) and 4(b) in PP#4F3074 (memo of A. Smith, 4/9/85) regarding the need for residue data for the forage and hay of small grain, or submit a revised Section B by imposing a grazing and feeding restriction. These deficiencies were discussed in person with Richard Conn of Ciba-Geigy on 5/6/87 who informed me that a revised label was submitted to PM team #21 on Oct. 20, 1986. After contacting PM team #21 (P. Hundeman) on 5/6/87, RCB received the revised label.

The following is the revised label statement "Do not graze livestock on treated areas or cut the treated crop for hay. Straw may be used for bedding", and "Highest yields are normally obtained when Tilt is applied at the time of flag leaf emergence (Feekes growth stage 8). Do not apply after this growth stage to avoid possible illegal residues."

Deficiency #1 (PP#4F3074, memo of A. Smith, 4/9/85) is resolved.

The petitioner must revise their feeding restriction in Section B to read "Do not graze or feed livestock on treated forage, or harvest treated crop for hay or silage." The "straw" statement may remain or be changed to "Straw may be used for feed or bedding." Tolerances will be recommended for straw and could be used for feed.

Livestock Dietary Exposure Assessment

Cattle and poultry feeding studies were discussed in PP#4F3074 (memo of A. Smith, 7/12/84). Residues of propiconazole in livestock tissues, milk, and eggs at various feeding levels and preslaughter intervals are discussed in detail in Table 1 above.

Assuming that the revised label resolved deficiencies #1, 4(a), and 4(b) discussed above, the remaining feed items from the proposed use in PP#4F3074 for cattle are the grains and straw of barley, rice, rye, and wheat. That for poultry are the grains of barley, rice, rye, and wheat. No feed items are involved in PP#4F3007 (pecans) and PP#4E3026 (bananas). Accordingly, the maximum dietary intake for dairy and beef cattle was calculated at 0.2 and 0.35 ppm, respectively and that for poultry at 0.07 ppm as shown below:

Feed Item	Proposed Tolerance (ppm)	Percent in Feed			Dietary Intake (ppm)		
		Dairy	Beef	poultry	Dairy	Beef	poultry
Wheat, grain	0.1	50	50	70	0.05	0.05	0.07
Wheat, straw	1.5	10	10	--	0.15	----	---
Rice, straw	3.0	--	10	--	----	0.30	---
					0.20	0.35	0.07

With the exception of the liver and kidney of cattle, there was no detectable propiconazole residues in the remaining meats, milk, and eggs at the lowest feeding level 15 ppm for cattle and 7.5 ppm for poultry. At the 15 ppm feeding level, propiconazole residues in the liver and kidney of cattle was quantitated at a maximum of 0.81 and 0.63 ppm, reflecting 21 day PSI for the liver and 28 day PSI for the kidney. At the second highest feeding level of 75 ppm for cattle and 37.5 ppm for poultry, it was apparent that propiconazole residues were detectable in meats, milk, and eggs. Therefore 40CFR§180.6(a)(2) applies; i.e., that it is not possible to establish with certainty whether finite residues will be incurred in the meats, milk, and eggs from the feed items in PP#4F3074, but there is a reasonable expectation of finite residues. Accordingly, the petitioner is advised to address deficiency #5 in PP#4F3074 (memo of A. Smith, 4/9/85) requesting proposing appropriate tolerances for livestock commodities. Specifically, the available residue data will support the following tolerances:

- 0.2 ppm for the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep.
- 0.1 ppm for the meat, fat, and meat byproducts (except liver and kidney) of cattle, goats, hogs, horses, poultry, and sheep.
- 0.1 ppm for eggs.
- 0.05 ppm for milk.

Other Considerations

Neither of the enforcement methodology, AG-454A and AG517, is capable of determining the free and conjugated compounds containing the triazole moiety contributed by propiconazole. Further, a deferral to TOX was made in connection with PP#4F3074 as to their concern regarding the toxicological significance of residues containing the triazole moiety. This question was discussed with Alan Katz of the Toxicology Branch on 5/1/87, in view of RCB's recent memo on the subject (PP#4F3074, memo of A. Smith, 12/31/86) concluding that background residues of the triazole-containing components appear at high and variable levels, and as such can mask the contribution of triazole due to treatment with propiconazole. Further, I indicated to Mr. Katz that the enforcement methodologies convert the parent and metabolites to 2,4-dichlorobenzoic acid and the residues are determined as parent using a conversion factor. The methods do not determine compounds containing the triazole moiety (without the 2,4-dichlorophenyl substituent) of propiconazole whether it is free or conjugate with the parent or metabolites (such as triazolealanine). There is, however, a method for such determination.

On May 12, 1987, a memo was received from the Toxicology Branch indicating that there is at this time no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for the triazole moieties contributed by propiconazole (memo of A. Katz, 5/8/87).

This resolves deficiency #5 in PP#4F3074 (memo of A. Smith, 4/9/85).

Conclusions

1. RCB concludes that the available livestock residue data previously generated using method AG-359 are valid.
2. The petitioner must revise their feeding restriction to read "Do not graze or feed livestock on treated forage, or harvest treated crop for hay or silage." The "straw" statement may remain or be changed to "Straw may be used for feed or bedding."
- 3(a). From the livestock feeding studies, it was apparent that propiconazole residues transfer to meat, milk, and eggs. Therefore 40CFR§180.6(a)(2) applies; i.e., that it is not possible to establish with certainty whether finite residues will be incurred in meat, milk, and eggs from the feed items in PP#4F3074, but there is a reasonable expectation of finite residues.

3(b). The petitioner must submit a revised Section F for PP#4F3074, proposing the following tolerances in lieu of the originally proposed 0.1 ppm for the kidney and liver of cattle, goats, hogs, horses, poultry, and sheep:

0.2 ppm for the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep.

0.1 ppm for the meat, fat, and meat byproducts (except liver and kidney) of cattle, goats, hogs, horses, poultry, and sheep.

0.1 ppm for eggs

0.05 ppm for milk

4. RCB is currently evaluating and reporting on the results of two method trials for Tilt, recently completed by the Analytical Chemistry Laboratory/COB/BUD in Beltsville. To allow the registrant's method to be used as an enforcement method, certain modifications are needed; these changes were relayed to Richard Conn of Ciba-Geigy by S. Malak on 4/29/87. A completed corrected copy of the enforcement method is needed for distribution to enforcement personnel.

5. A May 8, 1987 memo from Alan Katz of the Toxicology Branch states that residues containing only the triazole moiety (without the 2,4-dichlorophenyl substituent) need not be regulated at this time.

6. After resolving the deficiencies in Conclusions #2 3(b), and 4 above, RCB can recommend for the following tolerances for residues of propiconazole, originally proposed in PP#4F3074:

0.1 ppm for the grains of barley, rye, and wheat.

0.1 ppm for rice grain.

3.0 ppm for rice straw.

1.5 ppm for the straw of barley, rye, and wheat.

7. After resolving the deficiency in Conclusion 4 above, RCB will have no objections for establishing the following requested permanent tolerances:

° PP#4F3007: 0.1 ppm for Pecans.

° PP#4E3026: 0.2 ppm for bananas.

Recommendations

PP#4F3074: RCB continues to recommend against the requested tolerances for rice grain and straw, and small grains and their straws, and liver and kidney of livestock pending resolution of the deficiencies stated in Conclusions 2, 3(b) and 4 above. For a positive recommendation for the requested tolerances on small grains, the following is required:

1. A revision of the label restriction to read "Do not graze or feed livestock on treated forage, or harvest treated crop for hay or silage." The "straw" statement may remain or be changed to "Straw may be used for feed or bedding."
2. A revised complete copy of the proposed enforcement methods AG-454A and AG-517 as follows:
 - a. For Method AG-454A-page 9 #IIc.2.5: The "0.225 g crop equivalent (3 ml) aliquot" must be changed to "0.675 g crop equivalent (9 ml)."
 - page 11 #IIc.4.2: The partition with 15 ml of 10% diethylether/hexane must be repeated twice for a total of three extractions.
 - b. For Method AG-517-page 10 #IIc.2.5: The "0.225 g crop equivalent (3 ml) aliquot" must be changed to "0.675 g crop equivalent (9 ml)."
3. Propose tolerances for livestock commodities at the following levels:
 - 0.2 ppm for the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep.
 - 0.1 ppm for the meat, fat, and meat byproducts (except liver and kidney) of cattle, goats, hogs, horses, poultry, and sheep.
 - 0.1 ppm for eggs
 - 0.05 ppm for milk

PP#'s 4F3007 and 4E3026: RCB continues to recommend against the proposed tolerances in/on pecans and bananas until revised copies (as stated above) of the proposed enforcement methods are revised and determined to be acceptable.

cc: Circu, RF. SF (propiconazole, Banner®, Tilt®, or CGA-64250),
S. Malak, PP#4F3007, PP#4F3074, PP#4E3026, PM 21, and PMSD/ISB.
RDI:P. V. Errico:5/14/87:R. D. Schmitt:5/14/87
TS-769C:RCB:CM#2:RM814A:S.Malak:X557-4379:5/8/87:Revised 5/12/87.