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received
6-27-94
1:00 pm



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

JUN 16 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#2F4107. Difenoconazole (Dividend) in/on Wheat, and Animal RACs. Amendment of 5/18/94. MRID#s 432365-01, -02, & -03. Barcodes D203644 & D203645. CBTS# 13771 & 13772.

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6/27/94

And

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CIBA-GEIGY Corporation has proposed tolerances for residues of the fungicide difenoconazole [(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-[2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl]-1H-1,2,4-triazole on wheat, barley and animal RACs and as the result of seed treatment. This amendment addresses the deficiencies identified in the Memo of G. Kramer, 3/30/94. The revised tolerances with an expiration date of 12/31/98 now proposed are as follows:

Wheat Grain	--	0.1	ppm	Wheat Forage	--	0.1	ppm
Wheat Straw	--	0.1	ppm	Milk	--	0.01	ppm
Eggs	--	0.05	ppm	Fat	--	0.05	ppm
Meat	--	0.05	ppm	Meat By-Products	--	0.05	ppm

of cattle, goats, horses, hogs, poultry and sheep

In the Detailed Considerations section of this Memo, the outstanding deficiencies, listed as presented in the Memo of G. Kramer (3/30/94), are followed by the petitioner's response and our conclusions.

RECOMMENDATIONS

CBTS recommends against the proposed time-limited tolerances for difenoconazole on wheat and animal RACs for the reasons outlined in Conclusions 2, 3 and 5. ~~However, if the Metabolism Committee decides that the tolerance expression for difenoconazole should include the parent compound only, then a DRES analysis may be initiated~~ *now based on parent only.*

ECS 6/27/94

CONCLUSIONS

1. The only product chemistry data requirement that remains outstanding is the stability of the TGAI to metal ions (63-13). CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole.
2. The registrant reports that a confined crop rotation study has been completed and will be submitted in late June, 1994. Based on the results of this study, the registrant has added the following restriction to the Dividend label: "Do not plant any crop other than wheat within 120 days of planting wheat seed treated with Dividend." CBTS can not recommend in favor of such a rotational crop restriction until we review the actual study. **This deficiency will remain outstanding until we receive an acceptable confined rotational crop study or Section B is revised as requested in conclusion 2 from Memo, G. Kramer 3/30/94.** The label should restrict crop rotation to wheat by adding a statement such as "do not plant back any crops other than wheat within one year to fields in which treated seeds were planted."
3. All deficiencies in the wheat metabolism studies are resolved. CBTS can now refer to the Metabolism Committee on the toxicological significance of difenoconazole metabolites. A decision by CBTS concerning which residues to regulate will then follow. If a tolerance on the parent only is not appropriate, a revised Section F and additional field studies, analytical methodology, and storage stability data may be needed.
4. The nature of the residue in animals is considered understood for the purposes of this petition only. For any future petition in which there is a greater potential for transfer of residues to meat and milk, additional animal metabolism studies will be required.

5. A successful PMV of the proposed analytical enforcement method for animal RACs (Method AG-544) was conducted by ACL (Memo, G. Kramer 6/2/94). Several minor modifications of the method were requested. The registrant should submit a revised version of Method AG-544 as specified in conclusions 1-4 of Memo, G. Kramer 6/2/94. Until the receipt of the revised method, the requirements for analytical enforcement methodology will remain unfulfilled.

6a. The registrant has proposed that fulfillment of GLN § 171-4(e) (storage stability) be a condition for the granting of permanent tolerances and an unconditional registration for difenoconazole on wheat and animal RACs.

6b. Due to the apparent storage stability of difenoconazole in other RACs, CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole.

7a. The registrant has agreed to perform barley field trials and has withdrawn the proposed tolerances on barley RACs from Section F until such data is available. The registrant has also agreed to perform additional winter wheat trials. Based on the available wheat data from the U.S. and Europe in which negligible residues (below LOQ) were observed in wheat RACs, the registrant has requested a conditional registration and time-limited tolerances for difenoconazole and has proposed that fulfillment of GLN § 171-4(k) (crop field trials) be a condition for the granting of permanent tolerances and an unconditional registration.

7b. Due to the apparent negligible residues of difenoconazole in wheat RACs, CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole. We recommend that the planned field trials conform to the "EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances, 6/2/94." For barley, a total of 12 trials are required. If residues are below the LOQ, then only 9 barley trials will be required. For wheat, a total of 20 trials are required, or 15 if residues are below the LOQ. The registrant has already submitted the results of 11 acceptable field trials. CBTS suggests that the additional wheat trials be conducted in Region 2- 1 trial, Region 7- 3 trials and Region 8- 5 trials. Two independent samples from each plot should be collected and analyzed. All field trials initiated in 1995 or later will be expected to conform to the new guidance document. Hay is a RAC for both wheat and barley in Table II (June 1994). The registrant should thus collect and analyze hay samples from all field trials and propose tolerances for this RAC. Generally, if residues are below the LOQ, then only 15 wheat field trials would be required. In this case, CBTS is requesting 20 wheat trials since hay samples were not collected in the 11

previously submitted trials.

DETAILED CONSIDERATIONS

Deficiency - Conclusion 1a (from Memo, G. Kramer 3/30/94)

1a. While the petitioner has come up with reasonable scenarios for the formation of observed impurities, the possibility of other impurities that may result from additional side reactions should be discussed.

Petitioner's Response: Submission of:

Difenoconazole Technical (CGA-169374) Product Chemistry Data Requirements 61-3 (\$158.167). MRID# 432365-02

The registrant has provided a discussion of the formation of four possible impurities and the reasons why they are not found in the TGAI.

CBTS' Conclusion: The requested information has been provided. This deficiency is now resolved.

Deficiency - Conclusion 1b (from Memo, G. Kramer 3/30/94)

1b. In order to fulfill the requirements of Guideline 63-13, the registrant should submit further information on the procedure and results of experiments used to determine the stability of the TGAI to metals and sunlight and report on the stability of the TGAI to metal ions.

Petitioner's Response: Submission of:

Difenoconazole Technical (CGA-169374) Product Chemistry Data Requirements 63-13 (\$158.190). MRID# 432365-03

Stability to metals: The solid TGAI was stored in tin cans or exposed to strips of stainless steel, carbon steel and aluminum. Test samples were stored at room temperature or 38 °C. Samples were analyzed after 8, 16 and 26 weeks by visual inspection and GC analysis. No decomposition of the TGAI was observed.

Stability to sunlight: The solid TGAI was exposed to simulated sunlight (Xenon arc lamp) for 24 hours. Visual inspection and chromatographic analysis demonstrated that no decomposition of the TGAI had occurred.

Stability to metal ions: The registrant plans to prepare aqueous solutions/suspensions of the TGAI containing 10% of cupric, cuprous, ferric, ferrous, aluminum and zinc ions. The solutions will be stored for a minimum of 72 hours at room temperature and 38

°C. Samples will be analyzed by visual inspection and GC chromatography. The registrant has requested a conditional registration and time-limited tolerances for difenoconazole and has proposed that fulfillment of GLN § 63-13 be a condition for the granting of permanent tolerances and an unconditional registration.

CBTS' Conclusion: This deficiency is partially resolved. Only the stability to metal ions remains outstanding. CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole.

Deficiency - Conclusion 1c (from Memo, G. Kramer 3/30/94)

1c. Submission of a CSF for Dividend 3SF (in conjunction with PP#2E4051 - Memo, G. Kramer 1/10/94).

Petitioner's Response: "Dividend 3FS" is an old name for Dividend Fungicide. A CSF dated 5/18/94 for Dividend Fungicide was also included.

CBTS' Conclusion: The requested information has been provided. This deficiency is now resolved.

Deficiency - Conclusions 2b & 3 (from Memo, G. Kramer 3/30/94)

2b. The directions for use are adequate except that no crop rotation restrictions are specified. Until completion of the crop rotation studies (see below), the label should restrict crop rotation to barley and wheat by adding a statement such as "do not plant back any crops other than barley and wheat within one year to fields in which treated seeds were planted." A revised Section B is required.

3. The registrant has requested a waiver for rotational crop studies due to the anticipation of low residues in such crops as a result of the low application rate (equivalent to 0.34 oz. ai/A) and the short soil half-life. Based on the results of plant metabolism studies, it appears to be likely that a rotational crop planted 30 days after treatment (simulating crop failure) would contain significant (>0.01 ppm) residues. Another reason for these confined studies is to determine whether rotational crops are bioaccumulating soil metabolites of regulatory concern. This information can not be determined without actually performing the study. The registrant should provide the rotational crop studies for our review.

Petitioner's Response: A confined crop rotation study has been completed and will be submitted in late June, 1994. Based on the results of this study, the registrant has added the following restriction to the Dividend label: "Do not plant any crop other than wheat within 120 days of planting wheat seed treated with Dividend."

CBTS' Conclusion: CBTS can not recommend in favor of such a rotational crop restriction until we review the actual study. This

deficiency will remain outstanding until we receive an acceptable confined rotational crop study or Section B is revised as requested. The label should restrict crop rotation to wheat by adding a statement such as "do not plant back any crops other than wheat within one year to fields in which treated seeds were planted."

Deficiency - Conclusion 4b (1) (from Memo, G. Kramer 3/30/94)

4b(1). The registrant should provide chromatographic evidence of storage stability of the labelled grain, straw and forage samples.

Petitioner's Response: The registrant has provided a comparison of chromatograms of grain and straw samples that were analyzed initially and reanalyzed during work for the previous amendment. Comparison of these chromatograms reveals that no major changes in the metabolite profile occurred as a result of storage.

CBTS' Conclusion: The requested information has been provided. This deficiency is now resolved.

Deficiency - Conclusion 4b (2) (from Memo, G. Kramer 3/30/94)

4b(2). The registrant should further characterize the nature of the residue in the triazole-labelled seed-treated grain samples by performing the same procedures on the seed-treated grain samples as were performed on the foliar-treated samples and also further characterizing/identifying any fraction which contains >10% of the TRR or >0.05 ppm (i.e., Zones A, B and C from TLC separation). If there is insufficient radioactivity in these Zones for adequate identification/characterization, then the foliar-treated grain samples should be further characterized. The registrant must convince us that there is no single unidentified compound which exceeds these trigger values in the seed-treated grain sample.

Petitioner's Response: The registrant has argued that analysis of Zones A, B and D of the seed-treated grain is not necessary for the following reasons. Zone B (13.5% of the TRR) appears to be triazole alanine, Zone A (5.8% of the TRR) appears to be a mixture of free triazole and triazole alanine trapped with sugars at the origin and Zone D (18.7% of the TRR) appears to be partially derivatized triazole alanine. These identities, however, were not confirmed. Also, the registrant argues that the results of the metabolism studies conducted with seed-treatment in the field show that the levels of these metabolites (Zones A, B and D) are not significant. Two studies were performed using [¹⁴C]-difenoconazole in which wheat was seed-treated and grown in the field (MRID# 420900-34). The TRR in triazole-labelled mature grain was 0.024 and 0.135 ppm (Table 1). Extrapolation of results of the foliar-treated grain demonstrates that the maximum radioactivity in one of these zones in seed-treated grain grown in the field would be 0.025 ppm (Zone D, 18.7% X 0.135 ppm).

CBTS' Conclusion: CBTS accepts the argument that there could be no unidentified metabolites in the seed-treated, field-grown grain which would be present at >0.05 ppm. No further metabolite work on wheat grain is thus required. This deficiency is now resolved.

Table 1- TRR in wheat RACs as a result of seed treatment with phenyl- or triazole-labelled difenoconazole.

Site	RAC	Label	TRR (ppm)
Greenhouse	Forage (40 Day PHI)	Phenyl	0.075
		Triazole	0.148
	Forage (72 Day PHI)	Phenyl	0.016
		Triazole	0.010
	Straw	Phenyl	0.016
		Triazole	0.081
	Grain	Phenyl	0.003
		Triazole	0.583
Field (IL)	Forage (32 Day PHI)	Phenyl	0.095
		Triazole	0.007
	Forage (50 Day PHI)	Phenyl	0.008
		Triazole	0.010
	Straw	Phenyl	0.013
		Triazole	0.011
	Grain	Phenyl	0.004
		Triazole	0.024
Field (NY)	Forage (33 Day PHI)	Triazole	0.049
	Forage (62 Day PHI)	Triazole	0.053
	Straw	Triazole	0.059
	Grain	Triazole	0.135

Deficiency - Conclusion 4b (3) (from Memo, G. Kramer 3/30/94)

4b(3). The registrant should further characterize the nature of the residue in both the phenyl- and triazole-labelled whole plants harvested 40 days after planting.

Petitioner's Response: The registrant has argued that further analysis of forage is not necessary for the following reasons. Residues in forage were generally very low in the seed-treated plants, especially at intervals which correspond to the grazing restriction (55 days after planting). Samples from the study with the highest residues (greenhouse-grown, Table 1) were fractionated (Table 2). The soluble residues were separated on TLC. Identities of several compounds were assigned on the basis of their TLC mobility. These identities, however, were not confirmed. These results demonstrate that there could be no unidentified metabolites in the seed-treated forage present at >0.05 ppm.

Table 2- Fractionation and tentative identification of TRR in the forage (40 day PHI) of seed-treated wheat grown in the greenhouse.

Fraction/Metabolite	Label	ppm	% TRR
Organic	Phenyl	0.057	70.7
	Triazole	0.050	33.3
Aqueous	Phenyl	0.016	20.2
	Triazole	0.065	43.3
Bound	Phenyl	0.012	15.3
	Triazole	0.023	15.1
Difenoconazole	Phenyl	0.006	7.0
	Triazole	0.012	8.0
CGA-205375	Phenyl	-	-
	Triazole	0.035	23.0
Triazole Alanine	Phenyl	-	-
	Triazole	0.040	27.0
Triazole Acetic Acid	Phenyl	ND	ND
	Triazole	0.024	16.0
Total Identified	Phenyl	0.006	7.0
	Triazole	0.099	66.0

ND = Not Detected

CBTS' Conclusion: CBTS accepts the argument that there could be no unidentified metabolites in the seed-treated forage which would be present at >0.05 ppm. Also, the metabolite profiles in the triazole-labelled forage and straw samples are very similar. No further metabolite work on wheat forage is thus required. This deficiency is now resolved.

All deficiencies in the wheat metabolism studies are resolved. The major terminal residues in wheat grain are the metabolites triazole and triazole acetic acid; and in wheat straw and forage, are triazole alanine, triazole acetic acid and CGA-205375. The parent was not detected in grain and comprised 7-8% of the TRR in forage and 0.3-0.4% of the TRR in straw. CBTS can now refer to the Metabolism Committee on the toxicological significance of difenoconazole metabolites. A decision by CBTS concerning which residues to regulate will then follow. If a tolerance on the parent only is not appropriate, a revised Section F and additional field studies, analytical methodology, and storage stability data may be needed.

Deficiency - Conclusion 5b (from Memo, G. Kramer 3/30/94)

5b. The registrant has not provided the information we previously requested (Memo, R. Lascola 10/26/92). In order for CBTS to be able to determine the nature of the residue in animals, the petitioner must address the following concerns: a) The petitioner has failed to take all reasonable steps to identify or release aqueous phase and conjugated metabolites which comprise up to half of the observed activity in several tissues. The petitioner has not noted the effects of acidic or basic hydrolysis on these metabolites, nor has mass spectrometry been used to identify the metabolites. b) While the metabolite CGA-205375 appears to be the major organic-soluble metabolite, inconsistencies between the triazole- and phenyl-labeled experiments bring the measured residue levels of this compound into question. Specifically, bridge-intact metabolites should appear in approximately the same proportion in the two studies, and they do not. CBTS asks the petitioner to resolve these inconsistencies. c) The petitioner should also explain the large radioactivity recoveries (>>120%) reported for several samples. If the petitioner has stored extra samples from these studies under frozen conditions, reanalysis of the tissues may be attempted, taking care to address the concerns listed above. In that event, the petitioner should also supply information detailing the stability of the chemical and metabolites under the storage conditions. Otherwise, the petitioner will have to reconduct these studies.

Petitioner's Response: a) Further metabolite identification would require the repetition of these metabolism studies due to the age of the samples. b) Inconsistencies in the % of the TRR comprised of bridge-intact metabolites can be explained by differential transport of bridge-cleaved metabolites (i.e., free triazole). c) Experimental error lead to the apparent recoveries in excess of 100%. The registrant has committed to performing additional metabolism studies for any future registration in which there is a greater potential for transfer of residues to meat and milk. Based on the similarities of the metabolic fate of difenoconazole in

goats, hens and rats and on the low potential for transfer of residues to animal tissues, the registrant proposes that the nature of the residue is understood for the purposes of this petition.

CBTS' Conclusion: CBTS concurs with this argument. The nature of the residue in animals is considered understood for the purposes of this petition only. This deficiency is now resolved. For any future petition in which there is a greater potential for transfer of residues to meat and milk, additional animal metabolism studies will be required.

Deficiency - Conclusion 7b (from Memo, G. Kramer 3/30/94)

7b. We have forwarded the analytical method and ILV to the ACL, Beltsville for the PMV. CBTS will withhold its conclusion on the adequacy of method AG-544 as an analytical enforcement method for difenoconazole residues in meat, milk and eggs pending the outcome of the PMV.

Petitioner's Response: None required.

CBTS' Conclusion: A successful PMV was conducted by ACL (Memo, G. Kramer 6/2/94). Several minor modifications of the method were requested. The registrant should submit a revised version of the proposed analytical enforcement method for animal RACs (Method AG-544) as specified in conclusions 1-4 of Memo, G. Kramer 6/2/94. **Until the receipt of the revised method, the requirements for analytical enforcement methodology will remain unfulfilled.**

Deficiency - Conclusion 8b (from Memo, G. Kramer 3/30/94)

8b). Further studies are needed to demonstrate storage stability in the RACs wheat (or barley) grain and straw.

Petitioner's Response: Difenoconazole has previously been shown to be stable in tomatoes and potatoes for a minimum of 2 years of frozen storage and further storage stability studies in wheat grain and straw are planned. The registrant has requested a conditional registration and time-limited tolerances for difenoconazole and has proposed that fulfillment of GLN § 171-4(e) be a condition for the granting of permanent tolerances and an unconditional registration.

CBTS' Conclusion: Due to the apparent storage stability of difenoconazole in other RACs, CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole.

Deficiency - Conclusion 9b (from Memo, G. Kramer 3/30/94)

9b). CBTS concludes that this data is not adequate to support this request for domestic tolerances on wheat and barley RACs. The number of field trials and geographic representation is insufficient for winter wheat. In addition, the registrant failed to generate data for wheat hay, which may be reinstated as a RAC in Table II. Wheat hay was in the original Table II, but then deleted as announced in the FIFRA '88 Phase 3 Technical Guidance Package. It may be reinstated in the forthcoming revision of Table II. Also, data from barley field trials in the U.S. should be submitted to support tolerances on this crop. The registrant is requested to perform at least 4 barley field trials (in ND, MT, MN plus one other state such as ID, SD or WA) and at least 8 additional wheat field trials (in KS, OK, CO, NE and WA plus three other state such as MO, SD, MT, OH, IL or IN). Residue data for grain, straw and forage should be obtained in these trials. Data for and a revised Section F with proposed difenoconazole tolerances on wheat and barley hay may also be required in the future.

Petitioner's Response: The registrant has agreed to perform barley field trials and has withdrawn the proposed tolerances on barley RACs from Section F until such data is available. The registrant has also agreed to perform additional winter wheat trials. Based on the available wheat data from the U.S. and Europe in which negligible residues (below LOQ) were observed in wheat RACs, the registrant has requested a conditional registration and time-limited tolerances for difenoconazole and has proposed that fulfillment of GLN § 171-4(k) be a condition for the granting of permanent tolerances and an unconditional registration.

CBTS' Conclusion: Due to the apparent negligible residues of difenoconazole in wheat RACs, CBTS has no objection to allowing the fulfillment of this data requirement to be a condition of the requested conditional registration and time-limited tolerances for difenoconazole. We recommend that the planned field trials conform to the "EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances, 6/2/94." For barley, a total of 12 trials are required. The geographic distribution should be Region 1 or 2- 1 trial, Region 5- 3 trials, Region 7- 4 trials, Region 9- 1 trial, Region 10- 1 trial and Region 11- 2 trials. If residues are below the LOQ, then only 9 barley trials will be required. The geographic distribution should be Region 1 or 2- 1 trial, Region 5- 2 trials, Region 7- 3 trials, Region 9- 1 trial, Region 10- 1 trial and Region 11- 1 trial. For wheat, a total of 20 trials are required, or 15 if residues are below the LOQ. The registrant has already submitted the results of 11 acceptable field trials. These trials were conducted in Region 1- 1 trial, Region 4- 1 trial, Region 5- 3 trials, Region 6- 1 trial, Region 7- 1 trial, Region 8- 1 trial, Region 10- 1 trial and Region 11- 1 trial. CBTS suggests that the additional wheat trials be conducted in Region 2- 1 trial, Region 7- 3 trials and Region 8- 5 trials. Two independent samples from each plot should be collected and analyzed. All field trials initiated in 1995 or later will be expected to conform to the new guidance document. Hay is a RAC for both wheat and barley in Table II (June 1994). The registrant should thus collect and analyze hay samples from all

field trials and propose tolerances for this RAC. Generally, if residues are below the LOQ, then only 15 wheat field trials would be required. In this case, CBTS is requesting 20 wheat trials since hay samples were not collected in the 11 previously submitted trials.

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