



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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SEP 9 1992

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Memorandum

Subject: PP#1F3923: Cyfluthrin (**Bayocide**, **Baythroid**) Dermal Application to Cattle. Amendment of 4/28/92. CBTS# 9836. No MRID#. DP Barcode# D177681.

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To: John Hebert/George LaRocca (PM13)
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Miles, Inc., Animal Health Division, has submitted an amendment to their petition proposing increased tolerances for the pyrethroid cyfluthrin [cyano (4-fluoro-3-phenoxyphenyl) methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate] on cattle tissues (meat, fat, and meat by-products) at 0.4 ppm and milk at 0.08 ppm. This amendment is in response to the deficiencies outlined in our previous review of the petition (R. Lascola, 12/13/91) and reflects the agreements of a meeting between CBTS and Miles (R. Lascola memo of 3/16/92). In addition to the above permanent tolerances, Miles is also proposing interim tolerances (at the same residue levels) pending completion of previously requested dermal metabolism and residue concentration in milkfat studies.

Tolerances have been established (40 CFR §180.436) for residues of cyfluthrin in meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep (0.05 ppm), milk (0.01 ppm), cottonseed (1.0 ppm), and fresh hops (4.0 ppm). A temporary tolerance has been established for tomatoes. Numerous food and feed additive tolerances have also been established under 40 CFR §185.1250 and §186.1250. There are also several tolerances pending, including increased tolerances in animal products (1.5 ppm in meat, fat, and meat by-products, and 0.1 ppm in milk), in PP#9F3731/FAP#9H5574. The current petition is connected with the proposed registration of **Bayocide** Pour-On Insecticide (1% cyfluthrin) to control flies and lice on beef and dairy cattle (S. Hummel, EPA File Symbol 11556-RNT, 11/26/90).

Each deficiency from our previous review will be reiterated, followed by the petitioner's response and our comments.

Conclusions

- 1a. The petitioner has not submitted adequate information on the comparative qualitative aspects of dermal and oral metabolism of pyrethroids to support the proposed tolerances with expiration dates for cattle tissues and milk. The petitioner should submit this information to the Agency.
- 1b. The petitioner has agreed to conduct a dermal metabolism study for cyfluthrin applied to cattle. The results will be submitted 18 months after the conditional approval of the proposed registration. Deficiency 2 of the 12/13/91 memo remains unresolved pending receipt and review by CBTS of this study.
2. The petitioner's proposed study for determining the concentration of residues into milkfat is acceptable. The results will be submitted 12 months after the conditional approval of the proposed registration. Deficiency 4 of the 12/13/91 memo remains unresolved pending receipt and review by CBTS of this study.
3. The petitioner has submitted appropriate information concerning the eight isomers of cyfluthrin. Deficiency 6 of the 12/13/91 memo is resolved.

Recommendations

CBTS recommends against the proposed tolerances with expiration dates for the reason cited in Conclusion 1a. CBTS continues to recommend against the proposed permanent tolerances for the reasons cited in Conclusions 1b and 2, as well as Conclusion 5 of the 12/13/91 review.

Detailed Considerations

Deficiency 2 of 12/13/91 CBTS memo. There is no dermal metabolism study available to support this proposed pour-on use. A dermal metabolism study is needed to evaluate the requested tolerances for cattle. Cyfluthrin, ¹⁴C labeled in the cyclopropane and fluoromethyl ring should be used in separate studies.

Note: In the 3/12/92 meeting, EPA also indicated that "if Miles submitted adequate documentation describing the similarity of dermal and oral metabolism, we could recommend in favor of an interim tolerance provided that Miles also committed to performing the requested dermal metabolism studies necessary to complete the permanent tolerance request." (See R. Lascola memo of 3/16/92.)

Petitioner response. Miles has submitted "Bovine and Poultry Metabolism of Cyfluthrin and Three Related Pyrethroids (A Review of Available Information)", in order to establish the

similarity of the amounts and nature of the residues that occur in bovine and poultry tissue, milk, and eggs. The information presented is contained in "Regulatory Aspects of Pyrethroid Metabolism" by K. Arne and R. Perfetti, and also in several academic articles which are provided in an appendix.

The pyrethroids compared in this review are cyfluthrin, cypermethrin, deltamethrin, and permethrin. The data presented was obtained exclusively from metabolism studies in which the pesticide was orally administered to cattle or poultry. No dermal metabolism information is presented. Table 1 contains a summary of the percentage of parent pyrethroid residues in various matrices. Further information is also presented for the metabolic fate of the parent compounds in various tissues (degradation into acid or alcohol metabolites).

Table 1. Summary of Distribution of Parent Pyrethroid Residues.							
Pyrethroid	Log K _{ow}	Parent as Percent of Total Residues					
		Liver		Fat		Milk	Eggs
		Poultry	Cattle	Poultry	Cattle		
Cyfluthrin	5.6	13	86	79	> 90	98	62
Deltamethrin ¹	4.5	51	23	---	90	62 ³	51
Permethrin	3.5	22	5	81	60	69	57
Cypermethrin	3.4-3.6	16	5	59	80	90	72

1 - Deltamethrin information provided in Miles' submitted report.

2 - Values not reported for poultry. 3 - Levels of parent reported range from 16-62%.

Particularly highlighted is the relationship between higher octanol-water partition coefficient and the higher parent residues in fat and milk, and to a lesser degree in eggs. This relationship is much weaker for liver, probably due to the higher level of metabolic activity in that organ.

Miles also states that they agree to conduct a bovine dermal metabolism study. The data will be submitted within 18 months of the conditional approval of the registration of Bayocide (EPA Reg. No. 11556-RNT).

CBTS comments. Miles has shown that for the four pyrethroids shown, the parent compound is the major metabolite in fat, milk, and eggs. However, the petitioner has not addressed our major concern with regards to pyrethroid metabolism - that the **dermal** metabolism of cyfluthrin is similar to the **oral** metabolism. Miles discusses this issue only so far as to state that "significant differences due to oral and dermal dosing of animals have not been reported to our knowledge".

In their cover letter, Miles states, "We understood that although dermal metabolism data for other pyrethroid active ingredients were available, it was not appropriate for supporting the tolerances proposed in the petition for cyfluthrin". This statement is accurate with respect to the permanent tolerance. In the March 1992 meeting, several pyrethroids (including permethrin

and fluvalinate) were cited as having similar oral and dermal metabolic pathways. This information should be submitted to the Agency in support of the tolerances with expiration dates.

CBTS concludes that the petitioner has not submitted adequate information on the comparative qualitative aspects of dermal and oral metabolism of pyrethroids to support the proposed tolerances with expiration dates for cattle tissues and milk. The petitioner should submit this information to the Agency. We encourage the petitioner to continue their plans to conduct a dermal metabolism study for cyfluthrin, in support of the originally proposed permanent tolerances.

Deficiency 4 of 12/13/91 CBTS memo: Since there is evidence that cyfluthrin residues concentrate in fat, the petitioner should investigate the possible concentration of cyfluthrin into milkfat and submit the results of the study to the Agency. If the pesticide does concentrate in milkfat, the petition must also submit a revised Section F requesting an appropriate milkfat tolerance.

Petitioner response. "For the purposes of establishing a tolerance for milkfat, we propose that lactating cows be treated dermally with BAYOCIDE Pour-On (cyfluthrin) following the same application and sampling procedures as for residue studies already submitted (MRID# 415557-02). We also propose to analyze wholemilk and milkfat (as obtained by procedures described in PAM I, FDA) for residues of cyfluthrin. A tolerance would then be proposed for milkfat based on actual residue data." Miles also states that this residue data will be submitted within 12 months of the conditional approval of the registration of Bayocide (EPA Reg. No. 11556-RNT).

CBTS comments. Our previous review of this petition concluded that the potential for the above-mentioned residue study was adequate. Also, in our meeting with the petitioner, we had indicated that the PAM I procedures be used for this analysis, to accurately reflect the method by which residues in milk and milkfat would be determined. CBTS finds this proposal acceptable. Deficiency 4 remains unresolved pending receipt and review by CBTS of the completed study.

Deficiency 6 of 12/13/91 memo. The petitioner should submit a chemical name for cyfluthrin using the (RS) convention to identify the stereoisometry of each optically active site.

Petitioner response. "Cyfluthrin active ingredient consists of four isomeric pairs of enantiomers which are shown structurally in Attachment 1. The CAS nomenclature for cyfluthrin active ingredient (a mixture of all isomers and enantiomers) is cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. [CAS No. 68359-37-5].

"Each isomer pair has also been assigned a CAS number as follows for specific configurations:

[1 α -(R*), 3 α]-($\pm$) [CAS No. 86560-92-1]

[1 α -(R*), 3 β]-($\pm$) [CAS No. 86560-94-3]

[1 α -(R*), 3 α]-($\pm$) [CAS No. 86560-93-2]

[1 α -(R*), 3 β]-($\pm$) [CAS No. 86560-95-4]

"Each enantiomer has also been assigned a CAS number as follows:

1R-[1 α -(S*), 3 α] [CAS No. 85649-15-6]
 1R-[1 α -(R*), 3 α] [CAS No. 85649-12-3]
 1R-[1 α -(R*), 3 β] [CAS No. 85649-16-7]
 1R-[1 α -(S*), 3 β] [CAS No. 85649-19-0]
 1S-[1 α -(R*), 3 α] [CAS No. 85649-13-4]
 1S-[1 α -(R*), 3 β] [CAS No. 85649-17-8]
 1S-[1 α -(S*), 3 α] [CAS No. 85649-14-5]
 1S-[1 α -(S*), 3 β] [CAS No. 85649-18-9]

"It has been a practice of presenting the nomenclature of cyfluthrin active ingredient without specific stereoisomers indicated due to the presence of a mixture of eight different stereoisomers."

CBTS comments. The petitioner's submission is satisfactory. This deficiency is resolved.

CBTS notes the reference to cyfluthrin in the Merck Index (11th edition, 1989, p.432). The chemical name is given in (R,S) convention as (R,S)- α -cyano-4-fluoro-3-phenoxybenzyl-(1R,S)-*cis,trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Also, "Synthetic pyrethroid insecticide. Commercial product is mixture of 8 isomers, the (1R)-isomers primarily responsible for the activity."

Attachment 1: Chemical structures of cyfluthrin. (1 page.)

cc: R. Lascola, RF, Circulation, D. Edwards. PP#1F3923
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Cyfluthrin Active Ingredient - Isomers I + II + III + IV

