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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Lambda-cyhalothrin. Residue Transfer Study on Dairy Cattle with Analysis for Metabolite OH-CPA.

PP#'s 7F3560, 1F3952, 1F3992, 2F4109, 9F3770, 2F4114.
FAP#'s 0H5599, 1H5607.

DP Barcodes: D178587, D178588, D178590, D178591, D178593, D178595, D178596.

CB #'s 9915 through 9921. MRID # 423112-01.

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Background

The nature of the lambda-cyhalothrin residue in plants and animals is understood; however the regulatory status of the animal metabolite OH-CPA [3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid] has been uncertain because the metabolite has heretofore not been found in rats. CBTS and TB1 decided that unless the registrant, ICI Americas Inc., could show that OH-CPA was a rat metabolite, residue data on this metabolite and a validated analytical method would be needed before a final decision would be made about its inclusion in the tolerance expression (PP#9F3770, M. Flood, memo of 4/17/91). ICI subsequently submitted information which showed

that analogous metabolites of other pyrethroids have been found in rat urine, but we concluded that "There really is no direct analytical evidence that any of the minor metabolites found in the cyhalothrin rat study is HO-CPA." (FAP#0H5599, Mike Flood, memo of 3/23/92)

ICI has now submitted a magnitude of the residue study in dairy cattle that includes analyses for OH-CPA. The date of the submission is 5/11/92. Preliminary results were discussed in our 3/23/92 memo.

Conclusions and Recommendations

1. Results of the ruminant feeding study indicate that residues of hydroxymethylcyclopropanecarboxylic acid (OH-CPA) will be ≤0.01 ppm in kidney and liver when animals are dosed with 8 ppm lambda-cyhalothrin. (The maximum predicted concentration of lambda-cyhalothrin in the diet of cattle is lower than 8 ppm.) Results from two ruminant metabolism studies and one poultry metabolism study imply that residues in tissues other than kidney or liver will be non-detectable.

2. Based on results from the ruminant feeding study, three livestock metabolism studies, and the lower expected dietary intake of lambda-cyhalothrin in the diet of poultry, a new poultry feeding study is not warranted at this time. Only non-detectable residues are likely.

3. Due to the low levels of OH-CPA found in the tissue of ruminants, CBTS does not recommend that this compound be included in the tolerance expression.

Detailed Considerations

The following report has been submitted:

"Lambda-cyhalothrin (ICIA0321): Residue Levels of the Major Metabolites in Dairy Cows Fed on a Diet Containing the Insecticide," C.L. Eckstein and P.D. Francis, 5/6/92, Lab. Project No. LCYH-91-AT-01. (MRID # 423112-01)

Performing laboratories were ICI's Western Research Center, Richmond, CA and ABC Laboratories, Columbia, MO. The in-life portion of the study was conducted at Columbia, MO.

Twelve lactating Holstein cows were orally dosed with lambda-cyhalothrin for 28 days at 8 mg/kg (i.e., 8 ppm in the diet), 25 mg/kg, and 80 mg/kg. The 8 mg/kg level was based upon a preliminary estimate of the worst case animal feed residue. (In our 9/19/91 memo for PP#7F3560 a maximum dietary intake of

7.6 ppm lambda-cyhalothrin was estimated for beef cattle.) Four animals were maintained at each dosing level. An additional four animals served as controls. After 28 days of dosing, three cows from each treatment level were sacrificed and tissue samples taken. The remaining four cows were maintained for a 14 day depuration period before sacrifice. The group dosed at 80 mg/kg exhibited intestinal disorders, so the dose was lowered to 50 mg/kg. This resulted in the cows at the high dose rate receiving 55-60 mg/kg when averaged over the 28 day dosing period.

Liver and kidney were analyzed for lambda-cyhalothrin (ICIA0321), epimer (R157836), CPA (PP890) and OH-CPA ("Compound XI"). (Structures of these metabolites are give in our 9/19/91 memo for PP#7F3560.)

Analytical Methods

The analytical method for lambda-cyhalothrin and its epimer was ICI's Plant Protection Division Residue Analytical Method No. 86/1: "The determination of Residues of PP321 in Products of Animal Origin". The method, which has undergone EPA method validation, is summarized in our 9/19/91 memo.

The method for PP890 and OH-CPA, "Analytical Procedure for PP890 and Compound XI in Animal Tissue," is similar, but not identical, to ICI's "Method for Analysis of Lambda-Cyhalothrin Metabolites in Hops", also summarized in our 9/19/91 memo. Animal tissues are extracted with a 1:1 mixture of acetonitrile and water at pH 9. The extract is partitioned twice with hexane to remove lambda-cyhalothrin. An aliquot of the extract is taken and the acetonitrile is removed by rotary evaporation. To the resulting aqueous phase is added enough concentrated HCl to make the solution 2N HCl and the solution is refluxed for two hours to hydrolyze any conjugates present. The (nonpolar) metabolites are partitioned into dichloromethane and after removal of solvent are derivatized with trifluoroacetic anhydride and trifluoroethanol. Following derivatization, the analytes are partitioned into hexane and the sample is cleaned up by extraction on a Diol solid phase extraction cartridge. The analytes are eluted with 20% dichloromethane in hexane (v/v) and analyzed using capillary gas chromatography with a mass selective detector.

Percent recoveries from cow kidney and liver are given in Table 1. Representative chromatograms are acceptable.

Table 1

Percent Recoveries from Cow Kidney and Liver

Compound	Tissue	Fortification Range (µg/g)	% Recovery
ICIA0321	Kidney	0.0108-0.324	109.3±9.2
	Liver	0.0108-0.432	88.1±5.9
R157836	Kidney	0.0142-0.426	107.2±8.3
	Liver	0.0142-0.568	91.2±7.4
PP890	Kidney	0.01-0.1	92.4±9.8
	Liver	0.01-0.1	102.3±10.7
CPD XI	Kidney	0.01-0.1	97.4±15.5
	Liver	0.01-0.1	85.3±15.4

Storage Stability

Liver and kidney samples were analyzed for lambda-cyhalothrin and its epimer 140 to 260 days after sacrifice. Existing storage stability data are adequate to cover this interval (PP#7F3560, Mike Flood, memo of 9/19/91). Samples were analyzed for PP890 and OH-CPA up to 267 days after sacrifice. Storage stability was demonstrated by initially analyzing samples from the 60 mg/kg dose group at 42 days (kidney) and 20 days (liver) and then analyzing these samples over extended periods -- 225 days for kidney, 233 days for liver. No degradation was apparent. Almost all the samples were analyzed within these time periods. (Fortified samples were used to show no degradation in extracts.) We conclude that storage stability data are adequate.

Residue Data

Residues found in cow kidney and liver are given in the following two tables.

Table 2

Levels of Lambda-cyhalothrin, Epimer and Metabolites Found in Kidney [High Value (Average Value)]

	Residue (mg/kg)			
Dose Level (concentration in daily diet)	ICIA0321	R157836	PP890	CPD XI
8 mg/kg	0.08 (0.04)	0.01 (<0.01)	0.02 (0.01)	0.01 (<0.01)
25 mg/kg	0.12 (0.08)	0.02 (<0.01)	0.07 (0.04)	0.02 (0.02)
60 mg/kg	0.30 (0.25)	0.04 (0.04)	0.11 (0.06)	0.05 (0.02)

Table 3

Levels of Lambda-cyhalothrin, Epimer and Metabolites Found in Liver [High Value (Average Value)]

	Residue (mg/kg)			
Dose Level (concentration in daily diet)	ICIA0321	R157836	PP890	CPD XI
8 mg/kg	0.09 (0.03)	<0.01	0.02 (0.01)	0.01 (<0.01)
25 mg/kg	0.05 (0.02)	<0.01	0.06 (0.04)	0.04 (0.03)
60 mg/kg	0.09 (0.06)	0.02 (0.01)	0.15 (0.10)	0.08 (0.05)

Except for lambda-cyhalothrin found in kidney at 25 mg/kg feeding level, levels found in an earlier (1985) feeding study are comparable. These results are given in Table 4.

Table 4

Levels of Lambda-cyhalothrin and PP890 Found in Liver and Kidney -- 1985

	Residue (mg/kg)			
	ICIA0321		PP890	
Dose Level (concentration in daily diet)	Kidney	Liver	Kidney	Liver
5 mg/kg	0.01-0.07	<0.01-0.01	0.02	0.02
25 mg/kg	0.09-0.43	0.06-0.10	0.07	0.07

Comment

The study shows that at the 1X feeding level of lambda-cyhalothrin residues of the metabolites OH-CPA do not exceed 0.01 ppm. The study also shows that residue levels of this metabolite are generally lower than those of PP890 (CPA). We note that two ruminant metabolism studies -- including a dermal study -- and one poultry metabolism study showed lower levels of OH-CPA than corresponding levels of CPA. Solely on the basis of the poultry metabolism results, ICI argued that residue data on OH-CPA should not be required. The conclusion was rejected by CBTS (S. Willett, PP#7F3560, PP#7F3488, memo of 10/27/89). However, given the results of the ruminant residue transfer study, the results from three metabolism studies and the maximum predicted residues in poultry tissue -- see our memo of 9/19/91 -- we now conclude that a new poultry feeding study would produce little useful information. Hence, unless some new use results in a major increase of lambda-cyhalothrin in the daily diet, an additional poultry feeding study will not be required.

The question remains concerning possible inclusion of OH-CPA in the tolerance expression. CB1 and TB1 have concluded that other metabolites of lambda-cyhalothrin need not be included in the tolerance expression (P. Hurley, PP#7F3560, memo of 1/3/92). Regarding OH-CPA, however, we were only able to conclude that "It is...likely, but not certain, that hydroxymethyl cyclopropane-carboxylic acid and/or its conjugates are also rat metabolites of lambda-cyhalothrin." Nevertheless, given the low levels of OH-CPA present in ruminant tissue as well as the nature of a tolerance as a regulatory enforcement tool, CB1 strongly recommends against inclusion of this compound in the tolerance expression.

cc: PP#7F3560, PP1F3952, PP#1F3992, PP#2F4109, PP#2F4414, PP#9F3770, SF, RF, Circu., Mike Flood, E. Haeberer, Pam Hurley (TB1).

H7509C:CBTS:Reviewer(MTF):CM#2:Rm800A:305-6362:typist(mtf):8/28/92.
RDI:SectionHead:ETHaeberer:8/25/92:BranchSeniorScientist:RALoranger: 8/27/92.

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