11-17-92

Residue Chemistry Review

Comments:

Subject: PP#7F3488. Lambda-cyhalothrin. Label amendment request for Karate® on soybeans. CBTS# 9810. MRID#'s 422740-01, -02.

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Residue Chem: 860.1200 Directions for use
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Commodities: Soybean

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Reviewers: José J. Morales

Review Approver: Debra Edwards

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MEMORANDUM:

SUBJECT: **PP#7F3488**. Lambda-cyhalothrin. Label amendment request for Karate® (EPA Reg. No. 10182-96) on soybeans. DP Barcode D177185. CBTS# 9810. MRID#'s 422740-01, -02.

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Insecticide-Rodenticide Branch
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ICI Agricultural Products has submitted a proposal for amended use of Karate® (lambda-cyhalothrin) on soybeans to increase the use rate from 0.03 lbs. ai/A/application with a maximum seasonal rate of 0.05 lbs. ai/A/season to a maximum seasonal rate of 0.06 lbs. ai/A/season to allow two applications per season at 0.03 lbs. ai/A/application.

Tolerances with an expiration date of August 30, 1991 were established for lambda-cyhalothrin ([1alpha-(S), 3alpha-(Z)]-(±)-cyano-(3-phenoxyphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate) under 40 CFR §180.438 for the fat, meat and mbyp of cattle, goats, hogs, horses and sheep at 0.01 ppm; milk at 0.01 ppm; and cottonseed at 0.05 ppm. Raw Agricultural Commodities (racs) for which tolerances are pending include soybeans (PP#7F3488); wheat, sweet corn and sunflowers

(PP#7F3560/7H5543); broccoli, cabbage and tomatoes (PP#1F3952/1H5607); and head lettuce (PP#1F3985).

A food additive tolerance of 10.0 ppm in/on dried hops was recently established under 40 CFR §185.1310 as a result of FAP#0H5599 (57 FR 32440).

No permanent tolerances have been established for lambda-cyhalothrin on soybeans.

CONCLUSIONS

1. The manufacturing process of technical grade lambda-cyhalothrin has been adequately described. We do not foresee any residue problems from impurities in the technical. Although deficiencies pertaining to the written confirmation from the Chemical Abstract Service are resolved; CBTS recommends that the IUPAC names for lambda-cyhalothrin and its epimer (rather than the Chemical Abstract names) appear in the regulation, since in our opinion, a practicing chemist can more readily relate the IUPAC name to the structure (refer to M. Flood's memo of 9/19/91 (PP#7F3560/7H5543) and 3/23/92 (FAP#OH5599) for more details and the IUPAC names for lambda-cyhalothrin and its epimer).

2. The nature of the residue in plants and animals is adequately understood. The residue to be regulated is lambda-cyhalothrin, per se, and its epimer.

3a. ICI Method 81 for parent lambda-cyhalothrin and its epimer in plant matrices has undergone successful EPA method validation.

3b. ICI Method 86 for parent lambda-cyhalothrin and its epimer in animal matrices has undergone successful EPA method validation.

3c. Recoveries have been determined under FDA's multiresidue protocols for cyhalothrin, CPA [Cis-1-RS-3-(ZE-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid] and 3-PBAcid [3-phenoxybenzoic acid] (these recoveries were not listed in FDA's 11/2/90 summary).

4. Geographical representation of residue data is adequate for the proposed use on soybean seed.

5. The storage stability data of lambda-cyhalothrin on soybean seed are adequate to support the residue analyses for parent and epimer but not the metabolites. The petitioner needs to submit storage stability data of metabolites CPA, 3-PBAcid and 3-PBAlcohol for periods up to 26 months and in extracts for up to 42 days (the conclusion that the residue to be regulated consists only of parent and

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epimer was made under the assumption that the residue data on metabolites were accurate). CBTS has received a 24 month storage stability study and it is under concurrent review. This deficiency will remain unresolved until completion of the review by CBTS.

6. Residue data on soybean seed show that nondetectable (<0.01 ppm) residues were obtained after lambda-cyhalothrin treatment. No residue data were sent for soybean forage and hay. In the absence of residue data for these feed items, the registrant should impose a label restriction against feed use of forage and hay. A revised Section B is needed. Alternatively, the petitioner may submit residue data on soybean forage and hay in order to support the subject tolerance petition.

7. No data were sent on the storage stability of the processed commodities. The petitioner may either: submit storage stability data for lambda-cyhalothrin, its epimer, and metabolites for periods up to 10 months in soybean refined oil and meal; or resolve this deficiency as part of a concurrent CBTS review for PP#2F4109 (field corn) and PP#2F4114 (peanuts) by M. Flood.

8. A processing study on soybean seed indicates that residues of PP890 will be concentrated by at least 4X in soapstock. Residues of lambda-cyhalothrin, its epimer, and 3-PBAcid show no concentration in any of the processed commodities. There is no need for a feed additive tolerance since the only residues to be regulated are lambda-cyhalothrin and its epimer. However, the petitioner should be aware of this concentration factor in case the Agency decides to regulate any of lambda-cyhalothrin metabolites in the future.

9. Since residues of lambda-cyhalothrin per se are below the detection limit, we expect no increase in the dietary burden of ruminants and poultry. Therefore the original proposed tolerance of 0.01 ppm for parent per se in meat, fat, meat by-products and eggs of poultry is adequate for the proposed use on soybeans. However, we note that proposed uses on other racs would require an increase in ruminant tolerances [M. Flood's memo of 9/1/92 (PP#7F3560/7H5543 and PP#1F3992)].

RECOMMENDATION

CBTS recommends against the proposed amended use for reasons given in Conclusions 5, 6 and 7.

DETAILED CONSIDERATIONS

PRODUCT CHEMISTRY

The manufacturing process for lambda-cyhalothrin was submitted in support of PP#6F3318 (MRID# 401820-01) and discussed in S. Willett's memo of 9/29/87. There are no toxicological concerns for any of lambda-cyhalothrin impurities. Discussion about structure and isomers appears in M. Flood's memo of 9/19/91 (PP#7F3560/7H5543).

CBTS concludes that the manufacturing process of technical grade lambda-cyhalothrin has been adequately described. We do not foresee any residue problems from impurities in the technical. Although deficiencies pertaining the written confirmation from the Chemical Abstract Service are resolved; CBTS recommends that the IUPAC names for lambda-cyhalothrin and its epimer (rather than the Chemical Abstract names) appear in the regulation, since in our opinion, a practicing chemist can more readily relate the IUPAC name to the structure (refer to M. Flood's memo of 9/19/91 (PP#7F3560/7H5543) and 3/23/92 (FAP#OH5599) for more details and the IUPAC names for lambda-cyhalothrin and its epimer).

PROPOSED USE

The registered formulation of lambda-cyhalothrin proposed for use is Karate®. Karate® (EPA Reg. No. 10182-96) is an emulsifiable concentrate containing 13.1% of ai and 86.9% of inerts. This formulation contains 1 pound of active ingredient per gallon.

The following directions apply for soybeans: to control corn earworm, velvetbean caterpillar, green cloverworm, cabbage looper, saltmarsh caterpillar, woolybear caterpillar, cutworms, bean leaf beetle, mexican bean beetle, cucumber beetles, three-cornered alfalfa hopper, potato leafhopper and thrips apply 0.015 to 0.025 lbs. ai/A. For control of fall armyworm, yellowstriped armyworm, tobacco budworm, webworms, european corn borer, japanese beetle (adult), blister beetles, stink bugs, plant bugs, and grasshoppers apply 0.025 to 0.03 lbs. ai/A. For control of beet armyworm, soybean looper, lesser cornstalk borer, and spider mites apply 0.03 lbs. ai/A. Apply by scouting, usually at intervals of 5 or more days. Apply with ground or air equipment using sufficient water to obtain full coverage of foliage. When applying by air, apply in a minimum of 2 gallons of water per acre. Do not apply within 45 days of harvest. Do not apply more than 0.06 lbs. ai/A/season.

NATURE OF THE RESIDUE

Plants

Data on plant metabolism show that lambda-cyhalothrin is metabolized by cleavage of the ester linkage to form cyclopropane carboxylic acids and the corresponding phenoxybenzoic acid and/or 3-phenoxybenzyl alcohol (M. Flood's memo of 1/22/92, PP#7F3560/7H5543).

CBTS concludes that the nature of the residue in plants is adequately understood. The residue to be regulated is lambda-cyhalothrin, per se, and its epimer. CBTS and TOX have determined that plant metabolites need not appear in the tolerance expression at this time (M. Flood's memo of 1/22/92, PP#7F3560/7H5543).

Animals

Studies of lambda-cyhalothrin metabolism in ruminants and poultry have been reviewed in M. Flood's memo of 9/19/91. In addition to the plant metabolites, lambda-cyhalothrin animal metabolites include 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropane-carboxylic acid (OH-CPA) and 4-hydroxy-3-phenoxybenzoic acid (4'-OH-3-PBAcid) [M. Flood's memo of 12/26/91 (PP#1F3992)].

CBTS concludes that the nature of the residue in animals is adequately understood. The residue to be regulated is lambda-cyhalothrin, per se, and its epimer. CBTS and TOX have determined that animal metabolites need not to appear in the tolerance expression at this time [M. Flood's memo of 12/26/91 (PP#1F3992) and 8/31/92 (FAP#OH5599)].

ANALYTICAL METHODOLOGY

The analytical methodology used to determine the residues of lambda-cyhalothrin and its epimer in plant matrices is ICI Method 81, which was first described in MRID# 400540-01. Briefly, samples were extracted with acetone:hexane 1:1 (v/v), coextracted lipids were removed by liquid-liquid chromatography, followed by a florisil column to remove endogenous materials. The final determination is made by capillary GC with electron capture detection. The limit of determination is 0.01 ppm. This method has undergone EPA Method Validation for soybeans (PP#6F3318/PP#7F3488, E. Greer memo of 9/30/87).

The analytical methodology used for determination of lambda-cyhalothrin metabolites in plant matrices was submitted in FAP#0H5599 (MRID#416146-03). This method provides the co-analysis of cis and trans CPA (PP890). Lambda-cyhalothrin includes the cis isomer only. The trans configuration is in lower amounts, and it is believed to result from photoisomerization of the metabolite on the plant surface. The analysis of 3-phenoxybenzoic

acid (3-PBAcid) and 3-phenoxybenzyl alcohol (3-PBAlcohol) can be carried out by this methodology. 3-PB alcohol is oxidized to 3-PBAcid and the 3-PBAcid residue is quantified. Data are reported as the combination of 3-PBAcid and 3-PBAlcohol. Briefly, samples are extracted, filtered and subjected to a C_{18} solid phase extraction. The extract is rotoevaporated, concentrated with HCL and refluxed for 2 hours. After cooling, the extract is partitioned with organic solvent and the aqueous phase is discarded. Jones reagent (23 mL of concentrated sulfuric acid, 77 mL of water and 24g of chromium (VI) oxide) is added to the organic phase and after the reaction is carried out, the extract is diluted with water and partitioned with organic solvent. The organic layer extract is acid washed and then partitioned with tetraborate buffer (pH 9.0). The aqueous layer is retained, acidified, and partitioned with dichloromethane. The extract is evaporated to dryness and derivatized with trifluoroacetic anhydride and trifluoroethanol at 100°C for 5 minutes. This derivatized extract is analyzed by capillary GC using a mass selective detector. The limit of determination is 0.01 ppm.

The analytical methodology used to determine residues of lambda-cyhalothrin in animal matrices is ICI Method 86, reviewed in M. Firestone's memo of 1/22/86 (PP#6F3318). Parent lambda-cyhalothrin is extracted from milk or animal tissue with 50% acetone:hexane. The aqueous fraction is removed and the organic layer dried with sodium sulfate. The organic fraction is cleaned up by Florisil column chromatography prior to determination by packed column gas chromatography using a ^{63}Ni electron capture detector. The limit of determination is 0.01 ppm.

The analytical method used to determine lambda-cyhalothrin metabolites in meat, milk, poultry and eggs is ICI Method 96, which was first described in MRID# 417935-01. Briefly, samples are extracted with acetonitrile:hydrochloric acid or methanol. The extract is diluted with water, and parent lambda-cyhalothrin is removed on a C_{18}bonded silica cartridge. The eluate is evaporated and refluxed for 4 hours with HCL 4N. The hydrolysate is then partitioned into dichloromethane. For 3-PBAcid and/or 4'-OH-3-PBAcid analyses, the extracts are evaporated, reconstituted in 50% methanol and passed through a C_{18} column. The eluate is evaporated and redissolved in dichloromethane. 3-PBAcid is methylated with diazomethane prior to GC-MS with selected ion monitoring (SIM). CPA is benzylated with benzyl bromide and purified on a Florisil column prior to GC with electron capture detector. 4'-OH-3-PBAcid is quantitated using HPLC with electrochemical detection. The limit of determination is 0.01 ppm.

MULTIRESIDUE TESTING

The petitioner has determined recoveries of cyhalothrin, PP890 and 3-PBAcid under FDA's multiresidue protocols (PP#7F3488, S. Willett's memo of 3/15/88; PP#7F3560/7H5543, M. Flood's memo of 9/19/91). As of 11/2/90, results have not been listed in FDA's summary.

RESIDUE DATA

The original proposed use for Karate® on soybeans was the following: for the control of several pest insects, Karate® is to be applied at rates from 0.015 to 0.03 lbs. ai/A. The maximum seasonal application specified was 0.05 lbs. ai/A with a PHI of 45 days. The grazing of livestock and harvesting of foliage for forage or hay was prohibited. Field trials conducted in 1983 in Alabama, Arkansas, Delaware, Georgia, Illinois, Louisiana, Missouri, and Mississippi; in 1984 in Arkansas, Illinois, Indiana, Iowa, Louisiana, Maryland, North Carolina, and South Dakota; and in 1985 in Alabama, Iowa, Illinois, Georgia, Minnesota, and Mississippi receiving two applications of 0.03 lbs. ai/A (1.2X) or 0.15 lbs. ai/A (5X) with PHI's ranging from 27 to 65 days showed that nondetectable residues (<0.01 ppm) were obtained after lambda-cyhalothrin treatment (S. Willett's memo of 8/13/87).

Currently, residue data reflecting the application of lambda-cyhalothrin to soybeans appear in the following report:

> "Lambda-cyhalothrin (ICIA0321): Magnitude of the Residue Study on Soybean Seed"; J.C. Mckay; 5/30/91; Laboratory Project ID No. 0321-88-MR-14; Report No. RR 90-437B. Performing Laboratory was ICI Americas Inc. Western Research Center, Environmental Chemistry Analytical Section, Richmond, CA (MRID# 422740-01).

Six field trials were conducted during 1988 in Arkansas, Illinois, Iowa, Minnesota, North Carolina and Tennessee. According to Agricultural Statistics, 1988, these states accounted for at least 51% of the soybean production in the U.S. Two applications of lambda-cyhalothrin, using ground equipment, were made at a rate of 0.03 lbs. ai/A (1X); the first application at bloom and the last application 44 to 52 days before harvest. After collection, samples were frozen and shipped to either ICI Americas Inc. Eastern Research Center, Goldsboro, NC or ICI Americas Inc. Western Research Center, Richmond, CA. Analysis for residues of lambda-cyhalothrin and its epimer were conducted at Huntingdon Analytical Services, Middleport, NY. Analysis for residues of PP890, 3-phenoxybenzoic Acid (3-PBAcid) and 3-phenoxybenzyl alcohol (3-PBAlcohol) were conducted by Pharmacology and Toxicology Research Laboratory-West, Inc., Richmond, CA.

Considering the fact that lambda-cyhalothrin is a non-systemic insecticide, that a 45 day PHI is proposed, and that a similar use on the same crop yielded nondetectable residues, CBTS concludes that geographic representation of residue data is adequate for the proposed use on soybean seed.

Residues of lambda-cyhalothrin were shown to be stable when stored at -18°C for up to 26 months in commodities like peach, pea, oil seed rape, wheat grain, sugarbeet root, cottonseed, apple, cabbage and potatoes (PP#0H5599, M. Flood's memo of 9/19/91). To assess stability in extracts, 1:1 acetone:hexane extracts from the treated racs were held at

<4°C for 33 to 42 days after the 26 months analyses. No significant degradation was seen in these extracts. Samples of soybean seed were analyzed for lambda-cyhalothrin residues up to almost 21 months after sampling. Maximum interval between extraction and analyses was 26 days. Storage stability of metabolites PP890, 3-PBAcid and 3-PBAlcohol in 13 racs has been reported in PP#1F3952/1H5607. Metabolite residues were stable at -20 ± 10°C for 3 months. Data to support the stability of the metabolites for longer periods are being developed. Samples of soybean seed were analyzed for lambda-cyhalothrin metabolites PP890, 3-PBAcid and 3-PBAlcohol up to almost 24 months after sampling. Maximum interval between extraction and analyses was 1 day.

CBTS concludes that the storage stability data of lambda-cyhalothrin on soybean seed are adequate to support the residue analyses for parent and epimer but not the metabolites. The petitioner needs to submit storage stability data of metabolites CPA, 3-PBAcid and 3-PBAlcohol for periods up to 26 months and in extracts for up to 42 days (the conclusion that the residue to be regulated consists only of parent and epimer was made under the assumption that the residue data on metabolites were accurate). CBTS has received a 24 month storage stability study and it is under concurrent review. This deficiency will remain unresolved until completion of the review by CBTS.

Recovery data were obtained from untreated samples fortified with lambda-cyhalothrin at the level of 0.013 ppm to 0.21 ppm. Overall recoveries of 77% to 112% were obtained. Recovery data for lambda-cyhalothrin epimer at fortification levels of 0.017 ppm to 0.28 ppm were of 75% to 113%. Recovery data for metabolites PP890, 3-PBAcid, and 3-PBAlcohol at fortification level of 0.05 ppm ranged from 86% to 110% for PP890, 78% to 84% for 3-PBAcid, and 86% for 3-PBAlcohol. Submitted chromatograms show well resolved peaks in support of this data.

Table I summarize the amount of residues on soybean seeds resulting from 2 applications of lambda-cyhalothrin at the rate of 0.03 lbs. ai/A.

Table I. Lambda-cyhalothrin residues on soybean seeds

Study Location	PHI	ICIA0321 (ppm)[1]	R157836 (ppm)[2]	PP890 (ppm)[3]	3-PBAcid (ppm)[4]
TN	control	<0.01	<0.01	<0.01	<0.01
	44	<0.01	<0.01	<0.01	<0.01
AR	control	<0.01	<0.01	<0.01	<0.01
	45	<0.01	<0.01	<0.01	<0.01

Study Location	PHI	ICIA0321 (ppm)[1]	R157836 (ppm)[2]	PP890 (ppm)[3]	3-PBAcid (ppm)[4]
Il	control	<0.01	<0.01	<0.01	<0.01
	44	<0.01	<0.01	<0.01	<0.01
NC	control	<0.01	<0.01	<0.01	<0.01
	52	<0.01	<0.01	<0.01	<0.01
IA	control	<0.01	<0.01	<0.01	<0.01
	44	<0.01	<0.01	<0.01	<0.01
MN	control	<0.01	<0.01	<0.01	<0.01
	45	<0.01	<0.01	<0.01	<0.01

1. Lambda-cyhalothrin
2. epimer of lambda-cyhalothrin
3. cis-isomer
4. 3-Phenoxybenzoic Acid (combination of 3-PBAlcohol + 3-PBAcid)

Residue data on soybean seed show that nondetectable (<0.01 ppm) residues were obtained after lambda-cyhalothrin treatment. No residue data were sent for soybean forage and hay. In the absence of residue data for these feed items, the registrant should impose a label restriction against feed use of forage and hay. A revised Section B is needed. Alternatively, the petitioner may submit residue data on soybean forage and hay in order to support the subject tolerance petition.

PROCESSED COMMODITIES

Residues resulting from the processing of soybean seeds has been submitted in the following report:

> "Lambda-cyhalothrin - Magnitude of the Residue Study on Processed Soybean Products"; J.C. McKay; 10/23/91; Laboratory ID No. 0321-88-PR-06; Report No. RR 91-048B. Performing Laboratory was ICI Americas Inc. Western Research Center, Richmond, CA (MRID# 422740-02).

A field trial was conducted during 1988 in Arkansas. Two applications of lambda-cyhalothrin were made at a rate of 0.30 lbs. ai/A (10X); the first application was made 74 days

after planting and the last application 45 days before harvest. After collection, samples were frozen and shipped to the Food Protein Research and Development Center, College Station, TX, where they were processed into hulls, meal, crude oil, refined oil, soapstock (the complete processing procedure is given on page 14 of the report).

Samples were analyzed for lambda-cyhalothrin and its epimer within 9 months after sampling. Maximum interval between extraction and analysis was 3 days. Samples were analyzed for metabolites within 10 months after sampling. Maximum interval between extraction and analysis was 6 days. No data were sent on the storage stability of the processed commodities. The petitioner may either: submit storage stability data for lambda-cyhalothrin, its epimer, and metabolites for periods up to 10 months in soybean refined oil and meal; or resolve this deficiency as part of a concurrent CBTS review for PP#2F4109 (field corn) and PP#2F4114 (peanuts) by M. Flood.

Results are given in Table 2.

Table 2. Residues (ppm) of lambda-cyhalothrin and metabolites in processed soybean products

Commodity	ICIA0321 (ppm)[1]	R157836 (ppm)[2]	PP890 (ppm)[3]	3-PBAcid (ppm)[4]
seed	0.01	<0.01	<0.01	<0.01
hulls	<0.01	<0.01	<0.01	<0.01
meal	<0.01	<0.01	0.01	<0.01
crude oil	<0.01	<0.01	<0.01	<0.01
refined oil	<0.01	<0.01	<0.01	<0.01
soapstock	<0.01	<0.01	0.04	<0.01

1. Lambda-cyhalothrin
2. epimer of lambda-cyhalothrin
3. cis-isomer
4. 3-Phenoxybenzoic Acid (combination of 3-PBAlcohol + 3-PBAcid)

Based on the above residue data, residues of PP890 will be concentrated by at least 4X in soapstock. Residues of lambda-cyhalothrin, its epimer, and 3-PBAcid show no concentration in any of the processed commodities. There is no need for a feed additive tolerance since the only residues to be regulated are lambda-cyhalothrin and its epimer. However, the petitioner should be aware of this concentration factor in case the Agency decides to regulate any of lambda-cyhalothrin metabolites in the future.

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MEAT, MILK, POULTRY AND EGGS

Since residues of lambda-cyhalothrin per se are below the detection limit, we expect no increase in the dietary burden of poultry and ruminants. Therefore the original proposed tolerance of 0.01 ppm for parent per se in meat, fat, meat by-products and eggs of poultry is adequate for the proposed use on soybeans. However, we note that proposed uses on other racs would require an increase in ruminant tolerances [M. Flood's memo of 9/1/92 (PP#7F3560/7H5543 and PP#1F3992)].

cc: SF, RF, Circu., José J. Morales, M. Flood, E. Haeberer, PP#7F3488.

H7509C: Reviewer (JJM): CM#2: Rm 804-Q: 305-5010: typist (JJM): 11/10/92

RDI: E. Haeberer (11/12/92): M. Flood (11/12/92): D. Edwards (11/12/92)