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

AUG 15 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#7F3560/7H5543. KARATE* Insecticide (Lambdacyhalothrin or PP321) on Wheat, Sweet Corn & Sunflowers. Amendment of April 16, 1990. MRID # 414630-01 and -02. DEB # 6640 and 6641.

FROM: Leung Cheng, Chemist L. Cheng
Tolerance Petition Section II
Dietary Exposure Branch
Health Effects Division (H7509C)

THROUGH: Elizabeth T. Haeberer, Acting Section Head Elizabeth T. Haeberer
Dietary Exposure Branch
Health Effects Division (H7509C)

TO: G. LaRocca/A. Heyward, PM Team 15
Herbicide-Insecticide Branch
Registration Division (H7505C)

and

Toxicology Branch
Health Effects Division (H7509C)

In response to DEB's 2/3/88 review on the subject petition, ICI Americas has submitted the following:

1) a wheat metabolism study, and
2) a discussion of unidentified residues in the hen metabolism study.

The following 408 and 409 tolerances were proposed in PP#7F3560/7H5543 for residues of (±)-alpha-cyano-(3-phenoxyphenyl)-methyl (±)-cis-3-(Z-2-chloro-3,3,3-trichloro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate or lambdacyhalothrin:

wheat grain	0.01 ppm
sweet corn	0.01 ppm
sunflower seeds	0.03 ppm
poultry meat, fat and meat byproducts	0.01 ppm
sunflower hulls	0.07 ppm

sunflower oil	0.05 ppm

Tolerances for lambdacyhalothrin have been established under 40 CFR 180.438 for cottonseed at 0.05 ppm, for milk at 0.01 ppm and for the fat, meat, and meat byproducts of cattle, goats, hogs, horses and sheep at 0.01 ppm. These tolerances are not permanent and are due to expire on August 30, 1991.

ICI in this submission has stated that DEB at a meeting (9/27/88) concluded that a wheat metabolism study may satisfy the metabolism data requirement for cyhalothrin on wheat, sorghum and corn, and that the current wheat metabolism study, along with those previously reviewed metabolism studies on cotton/cottonseed, soybeans, and cabbage, may support use of cyhalothrin on sunflowers, peanuts, onions, tomatoes and alfalfa.

Also, in its cover letter dated 4/16/90, ICI has stated that "this resubmission addresses all the deficiencies that RCB earlier identified with regard to the tolerances on sweet corn and sunflowers. As such, ICI anticipates that DEB will concur with ICI's request for tolerances in/on sweet corn and sunflowers."

ICI will submit additional data to support the proposed tolerance on wheat at a later date.

CONCLUSIONS

1. DEB is unable to conclude the adequacy of the submitted wheat metabolism study at this time. Refer to pages 5-6 (items a through g) of this review for additional information or explanation requested concerning this study.

Consequently, DEB is unable to recommend in favor of establishing tolerances on sweet corn and sunflowers at this time.

2. The primary terminal residues of concern in poultry are the same as those in ruminants: PP321 and its metabolites CPA [3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylic acid], OH-CPA [3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylic acid], 3-PBAcid [3-phenoxybenzoic acid] and 4-OH-3-PBAcid [4-hydroxy-3-phenoxybenzoic acid].

However, as stated in our (S. Willett) 10/27/89 memo, the final decision as to which metabolites must be regulated on a permanent basis will be made by the HED Metabolism Committee.

3. Additional data to support the proposed tolerance on wheat will be submitted at a later date.

RECOMMENDATION

DEB cannot recommend in favor of establishing tolerances for residues of lambdacyhalothrin on wheat, sweet corn and sunflowers because of Conclusion 1, 2 and 3.

1) Wheat metabolism (MRID # 414630-01)

In our 2/3/88 review, it was concluded that "[t]he nature of the residue in small grain crops is not adequately delineated and is acceptable in oil seed crops (cotton and soybeans) for certain specified uses only." Furthermore, the review stated that "a good metabolism study on wheat at sufficiently exaggerated rates to confirm or deny translocation of 14C metabolites into grain or their existence in wheat straw is needed."

The submitted wheat metabolism study was conducted at Jealott's Hill Research Station, Bracknell, Berkshire, England.

Carbon-14 lambdacyhalothrin that was labeled in the cyclopropane ring (acid label) and labeled in the phenoxy ring (alcohol label) were employed. The company code for lambda-cyhalothrin is PP321.

Three plots (plot A, B, or C) of winter wheat were treated with either acid label PP321 or alcohol label PP321. For plot A, two applications of radiolabeled PP321 were made, the first being made at first emergence and the second just prior to ear emergence, resulting in a total of 0.387 lb ai/A for the acid label and 0.373 lb ai/A for the alcohol label. Fourteen days after the second application, immature wheat grain was harvested.

For plot B, the same treatment regime was employed. Total amount applied were 0.373 lb ai/A for the acid label and 0.373 lb ai/A for the alcohol label. However, wheat was left to mature and harvested 85 days after the second application.

For plot C, three applications were made. The first two applications were made at the same time as those for plot A and plot B, with the third application about 50 days after the second treatment (total 0.535 lb ai/A acid label and 0.588 lb ai/A alcohol label). Wheat was harvested 30 days after the third application.

Also, wheat was harvested from an untreated area of similar size some distance from the treated areas at each harvest interval to act as a control.

Representative subsamples of immature and mature grain were extracted with hexane, acetonitrile, aqueous acetonitrile, ethanol or methylene chloride. Activities in these extracts were measured by LSC. Subsamples of the dried remaining residues were combusted

to determine the amount of radioactivity unextracted. The cumulative amounts of PP321 applied and the total radioactive residue levels on immature (plot A) and mature wheat grain (plot B and C) are tabulated below.

	lb ai/A	acid label	alcohol label
plot A	0.387, 0.373	0.002 ppm	0.007 ppm
plot B	0.373, 0.373	0.018 ppm	0.005 ppm
plot C	0.535, 0.588	0.131 ppm	0.112 ppm

Both samples of immature grain from plot A and the alcohol label sample of mature grain from plot B were not further analyzed after extraction. Extraction and analysis of the remaining 3 samples are described in more detail below.

Extracts were analyzed by TLC. Authenticated reference standards were run alongside and admixed with aliquots of the extract. Two solvent systems were employed for the characterization of metabolites in these extracts (cyclohexane saturated with formic acid: diethyl ether, 3:2 (v/v), hexane:ethyl acetate:acetic acid, 70:30:2 (v/v/v)).

Plot C (30 day PHI)

The two wheat grain samples from plot C were extracted according to Figures 1 and 2 (Attachment). For the alcohol label, fractions A, B and D represented 80.2%, 5.1% and 6.4% of the total radioactive residue (TRR) in wheat grain, respectively. These fractions were analyzed by TLC in the 2 solvent systems mentioned above. Based on autoradiograms and radioscans of the TLC's, fraction A was determined to be essentially all (96.3%) undegraded PP321 plus its isomers; fraction B to be 74.9% PP321 plus its isomers and 2.6% 3-phenoxybenzoic acid (compound V); fraction D to be 65.8% PP321 plus its isomers and 11.4% 3-phenoxybenzoic acid. A minor fraction labeled as "polar material" was also observed in fraction B (6.9%, 4 components, and in fraction D (5.4%, 4 components). In summary, residues in mature grain (0.112 ppm) were characterized to be primarily undegraded PP321 and its isomers (83%) and 3-phenoxybenzoic acid (0.8%). None of the remaining individual fractions exceeded 5% of the TRR.

For the acid label (see Figure 2 for the extraction scheme), fractions H and I accounted for 76.3% and 5% of the TRR in wheat grain. TLC analysis showed that fraction H was essentially all PP321 and its isomers (95.6%) and fraction I consisted of primarily 74.2% PP321 and its isomers and 4.6% cis acid (compound Ia); the trans acid (compound Ib) and hydroxylated acid (cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylic acid, compound XI) were not detected. In summary, mature grain (0.131 ppm) in this case primarily consisted of 76.4% PP321 plus its isomers and 0.2% of the parent cis acid (compound Ia). None of the remaining individual fractions

exceeded 8% of the TRR.

Fraction A from the alcohol label experiment and fraction H from the acid label experiment were also analyzed by HPLC. Chromatograms confirmed these 2 fractions to be lambdacyhalothrin (79.8-83.4%) and 7 other pairs of enantiomers (15.9-17.1%). The chemical purity in these 2 fractions was determined to be 96.9% for fraction A and 99.3% for fraction H.

Plot B (85 day PHI)

Wheat grain (0.018 ppm) harvested from the acid label experiment was extracted according to the scheme shown in Figure 3. Fraction U (17.8% of TRR) was analyzed by TLC to be 1.3% PP321 (and its isomers), 16.6% cis acid Ia, 8.6% trans acid Ib, 14.2% hydroxylated acid (cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylic acid, compound XI), 6.7% "polar material" and 52.6% of up to 9 unknowns (with no individual component at greater than 16.5%).

Wheat grain (0.005 ppm) from the alcohol label showed a activity distribution of 37.8% extractable and 62.2% unextractable. It was not characterized by TLC, probably due to the low activity.

Plot A (14 day PHI)

Grain samples from the acid label and alcohol label experiments contained low activity (0.002 ppm and 0.007 ppm). Residues were not further analyzed after extraction (56.9% and 72.2% extractable).

DEB comments

Before DEB can conclude on the adequacy of the submitted wheat metabolism study, ICI needs to provide explanation and additional information concerning this study.

a. The term "ear emergence" needs to be defined.

b. The total recovered radioactivity on wheat grain was obtained by summing the counts in the solvent extracts and combustion analysis on the residue after extraction. In order to demonstrate that activity was not lost during the extraction process, combustion data on the harvested wheat grain samples prior to any fractionation manipulation must be provided.

c. Wheat plants in plot A and plot B were twice sprayed with acid label PP321 or alcohol label PP321, both on the same days and at the same growth stages. The total amounts applied were virtually the same (0.373 or 0.383 lb ai/A to plot A versus 0.373 lb ai/A to plot B). Wheat grains from plot B were allowed to mature and were harvested 85 days after the second application whereas wheat grains

from plot A were not allowed to mature and were harvested 14 days later. Thus, a higher level of radioactivity would be expected in the immature grains harvested soon after treatment (14 days PHI) from plot A. Yet the results indicate that there is an increase in the acid label experiment (0.002 ppm vs 0.018 ppm).

d. The total amounts of PP321 applied to wheat plants in plot C were higher than those in plot B (1.43x acid label and 1.58x alcohol label). While higher levels of radioactivity would be expected from wheat plants in plot C because of a shorter PHI (30 days vs 85 days), the difference in the two levels seems excessive (7x in the acid label and 22x in the alcohol label).

e. Wheat plants in plot B received 2 applications of PP321, one prior to ear emergence and the second one at ear emergence. Data from plot B experiment showed substantial degradation of PP321 to cis acid Ia, trans acid Ib and hydroxylated acid XI when mature grains were harvested 85 days after the second treatment. Wheat plants in plot C received a third application in addition to the 2 treatments made on the same 2 days when PP321 was applied to plot B plants. Yet, residue analysis of plot C wheat grains showed only undegraded PP321 and cis acid Ia; the trans acid Ib and the hydroxylated compound XI were not detected.

f. Data thus far indicate that PP321 degrades extensively 85 days after application (Plot B experiment). In the acid label experiment, the only analyzed fraction (Fraction U) represents ca 18% of the TRR in wheat grain. Other terminal fractions include: a dichloromethane fraction containing 2.2% TRR, acid fraction (56.6%) and solid residue fraction (10.6%, see Fig 3) and TLC analysis data were not provided for these 3 fractions. Since activity in the "acid fraction" accounts for more than 50% of the TRR in grain, the registrant should provide TLC analysis on this fraction. Attempts should also be made to identify or characterize the component(s) in this fraction.

g. Wheat straw may be fed to livestock and is a major feed item. Metabolism data on wheat straw need to be provided.

2) Metabolism in Laying Hens (MRID # 414630-02)

In our review of 2/3/88, the reviewer concluded that the identity of chromatogram spots (10% in egg yolk and 12% in liver) from the acid label study need to be discussed.

In response, ICI submitted the following discussion. For egg yolk, the registrant stated that, after exhaustive extraction, 71% of the activity in the egg yolk was extracted into acetonitrile. The unidentified fraction comprised 10% of the extract. The unidentified fraction therefore comprised only 7.1% (10% x 71%) of the TRR in egg yolk. ICI also referenced a journal article (title

6

of journal unknown) in which the ratio of egg yolk to albumen was found to be 1:2. As a result, on a whole egg basis, the unidentified spot on the chromatogram occupied 2.4% of the egg TRR (7.1% x 1 part yolk / 3 parts whole egg). Both of these values are below the "trigger" value of 10% recommended in the Phase III Guidance document. The concentration (0.014 ppm) of the unidentified residue in egg yolk falls within the range that the partitioning behavior between aqueous and an organic solvent should be determined by TLC, HPLC analysis of the organosoluble activity. Also, 61% of the TRR in egg yolk was characterized as PP321.

The registrant also provided calculations which showed the level of this unidentified residue would be 0.0053 ppm on a whole egg basis and thus would not be detected with a limit of detection of 0.01 ppm. Since hens in this metabolism study were dosed at a concentration equivalent to 10.8 ppm acid label PP321 in the feed, in order for this unknown to be detected in eggs, the hen diet would need to contain 20.4 ppm PP321 (10.8 x 0.01 / 0.0053). Based on a hypothetical poultry diet (consisting of 25% alfalfa at 3 ppm, 60% sorghum and corn grain at 0.5 ppm, 3% wet tomato pomace at 1.5%, and 12% sunflower meal at 0.03 ppm; see 10/27/89 memo, S. Willett) the highest concentration of PP321 currently expected in hen diet would be 1.1 ppm.

With respect to the 12% unidentified spot in chicken liver, ICI presented a similar line of argument. This unknown, on a TRR basis, is in fact 9.6% (80% extractable x 12%). Since the TRR in liver was 0.43 ppm, the concentration of this unknown was therefore 0.041 ppm. Using the 0.01-0.05 ppm concentration criterion recommended in the Guidance document, TLC characterization would be adequate. ICI pointed out that the cis acid (compound Ia) comprises about 50% of the TRR in liver and is thus the primary metabolite; the unidentified metabolite is a minor metabolite in liver. In addition, for this liver unknown to be detected hens would have to be exposed to 2.6 ppm PP321 in their diet as opposed to the current worst case exposure of 1.1 ppm.

DEB comments

ICI is correct that the unidentified unknown in egg yolk accounts for less than 10% of the TRR. Since more than 61% TRR in egg yolk had been characterized (as PP321 plus isomers) DEB concludes that no additional analytical work is required.

For liver, in addition to the 50% TRR characterized as compound Ia (cis acid), 10-13% of the liver activity was determined by TLC to be compound XI (hydroxylated cis acid). The unidentified component in the liver also accounts for <10% of the TRR. DEB thus concludes that no additional metabolism work is required on the liver.

Therefore, the primary terminal residues of concern in poultry

are the same as those in ruminants: PP321 and its metabolites CPA [3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylic acid], OH-CPA [3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropane-carboxylic acid], 3-PBAcid [3-phenoxybenzoic acid] and 4-OH-3-PBAcid [4-hydroxy-3-phenoxybenzoic acid].

However, as stated in our (S. Willett) 10/27/89 memo, the final decision as to which metabolites must be regulated on a permanent basis will be made by the HED Metabolism Committee.

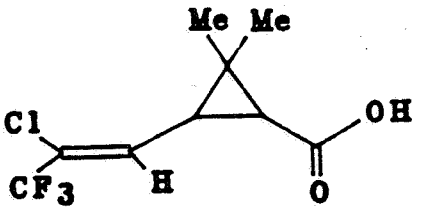
Attachment (4 pages): chemical structures, extraction schemes

cc:Circ, RF, PP#7F3560/7H5543, Cheng, PIB/FOD
RDI:ETHaeberer:8/14/90:RALoranger:8/14/90
H7509C:DEB:LCheng:CM#2:RM810:8/9/90:8/14/90:02:

8

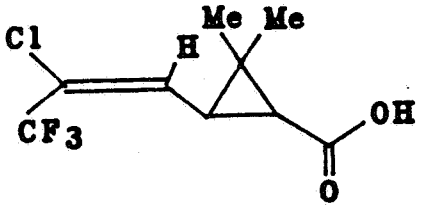
ATTACHMENT

Compound Ia



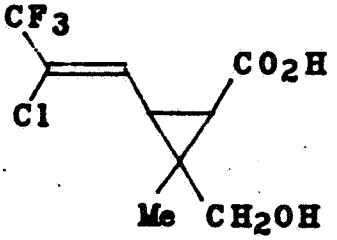
(1RS)-cis-3-(ZE-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid.

Compound Ib



(1RS)-trans-3-(ZE-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid.

Compound XI



cis-3-(2—chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylic acid.

Page _____ is not included in this copy.

Pages 10 through 12 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.