

file

Shaughnessy No: 128897

Date Out of EAB: JAN 27 1988

To: George LaRocca/C. Dively
Product Manager #15
Registration Division (TS-767)

From: Emil Regelman, Supervisory Chemist
Review Section #3
Exposure Assessment Branch
Hazard Evaluation Division (TS-769)



Thru: Paul F. Shuda, Chief
Exposure Assessment Branch/HED (TS-769C)



Attached, please find the EAB review of...

Reg./File # : 10182-OA

Chemical Name: PP 321

Type Product: Insecticide

Product Name: KARATE IEC

Company Name: ICI Americas Inc.

Purpose: Comments on summary of meeting with ICI to discuss
previous data review.

Action Code(s): 101 EAB #(s) : 80084

Date Received: 11/02/87 Total Reviewing Time: 1.6 days

Date Completed: _____

Deferrals to: _____ Ecological Effects Branch
_____ Residue Chemistry Branch
_____ Toxicology Branch

1. CHEMICAL: Common name: None

Chemical name: (+)-alpha-cyano-(3-phenoxyphenyl)methyl(+)-
cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)
-2,2-dimethylcyclopropanecarboxylate.

Trade name(s): Karate, (PP321 is the active ingredient)

Formulations: 1 lb/gal EC

2. TEST MATERIAL: N/A, No new data were submitted.

3. STUDY/ACTION TYPE: Review of registrant's letter containing a summary of a meeting held on October 15, 1987 concerning data submitted in support of the registration of PP321 for use on cotton.

4. STUDY IDENTIFICATION: ICI Letter of October 26, 1987. Summary of a meeting held on October 15, 1987 with representatives of ICI at which data submitted in support of the registration of PP321 (Karate) for use on cotton were discussed.

5. REVIEWED BY:

Arthur Schlosser
Chemist
EAB/HED/OPP

Signature: January 22, 1988
Date: Arthur O. Schlosser

6. APPROVED BY:

Emil Regelman
Supervisory Chemist
Review Section #3, EAB/HED/OPP

Signature: [Signature]
Date: JAN 27 1988

7. CONCLUSIONS: The registrant's summary is generally accurate and reflects the discussions which took place at the meeting of October 15. with the following exceptions: concerning the confined rotational crop study, EAB questioned the procedure of exposing control plants to $^{14}\text{CO}_2$ and the lack of any attempt by the reseachers to identify plant residues.
Reentry questions were not discussed at the meeting since the EAB expert was not present.

8. RECOMMENDATIONS: We concur with ICI's summary of the meeting of October 15 with the exception of some matters concerning the confined rotational crop study (see conclusions). No decisions as to the acceptability of any data discussed were made at the meeting. However, EAB agreed to consider all of the registrant's arguments when they are submitted in writing. Reentry matters were not discussed at the meeting; they will be addressed separately in a memo to Ms. C. Dively.
9. BACKGROUND: A meeting was held on October 15, 1987 between registrant (ICI Americas Inc.) and OPP (HED/EAB and RD) personnel to discuss the comments made in EAB# 70233 (September 17, 1987) on data submitted to support the use of PP321 (Karate) on cotton.
10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES: The registrant has asked for EAB comments on the written summary of the meeting held on October 15, 1987. See ICI Americas letter of October 26, 1987.
- A. Crop Rotation (Confined). While the summary given is generally accurate, EAB commented that the control samples should not have been exposed to $^{14}\text{CO}_2$, plant residues should have been chemically identified, and data on net plant residues should have been formally presented.
- B. Anaerobic Soil Metabolism. This is still a data gap. A study submitted earlier is still under review which should be completed shortly.
- C. Fish Accumulation. The summaries, explanations and supplementary data provided are generally accurate and reflect the comments made at the meeting.
- D. Adsorption/Desorption (batch equilibrium). The summary and explanation given are accurate and reflect the comments made at the meeting.
- E. Reentry. The registrant questions the need for reentry data to support the use of PP321 on cotton. Reentry matters were not discussed at the meeting of October 15 since the EAB expert on reentry concerns was not present at this meeting. A response to the registrant's comments on reentry will be sent separately by memo to Ms. C. Dively of RD.
- No decision was made at the meeting as to the acceptability of any of the data discussed. EAB agreed to consider each of the arguments presented by ICI when they are officially submitted in writing.
11. COMPLETION OF ONE-LINER: Not applicable to this action.
12. CBI APPENDIX: Data submitted appear to be CBI and should be treated as such.



ICI Americas Inc.

COPY 2

Agricultural
Products

FEDERAL EXPRESS

October 26, 1987

Ms. Christine A. Dively
Product Management Team (15)
Insecticide-Rodenticide Branch
Registration Division (TS-767C)
U.S. Environmental Protection Agency
Crystal Mall 2, Room 200
1921 Jefferson Davis Highway
Arlington, VA 22202

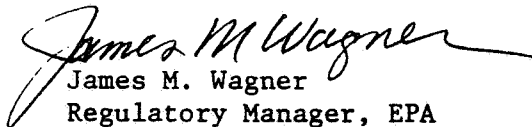
Dear Ms. Dively:

RE: KARATE® Insecticide for Cotton
EPA File No. 10182-OA

Thank you for arranging the meeting with Exposure Assessment Branch on October 15. The meeting was very helpful to ICI as it allowed us to address each of EAB's concerns and to receive feedback from the Agency.. As a result, we anticipate that all outstanding issues with EAB will be resolved through a written submission of ICI positions given at the meeting (to be submitted in about 1 week).

I have prepared and enclosed copies of a summary of the meeting for you and Mr. Schlosser in EAB. If either of you have any comments on this summary, please let me know.

Sincerely,


James M. Wagner
Regulatory Manager, EPA

JMW:ehl
T1/102687EHL01

Enclosures



OCT 27 1987

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**SUMMARY OF MEETING BETWEEN ICI AND EPA
October 15, 1987 at Washington, D.C.**

**Subject: KARATE INSECTICIDE for Cotton
EPA File Symbol 10182-OA**

Participants:

**EPA - Mr. Arthur Schlosser, Exposure Assessment
Branch**

Ms. Christine Diveley, Registration Division

**ICI - Dr. Ian Hill, ICI, UK
Mr. David Bewick, ICI, UK
Dr. Nazim Punja, ICI, UK
Mr. James Wagner, ICI, Wilmington, Delaware**

Background:

On October 24, 1985, ICI submitted a registration application and tolerance petition for the new active ingredient PP321, which is contained in the product KARATE Insecticide. On October 29, 1986, ICI received the Exposure Assessment Branch (EAB) review comments for this petition. This review pointed out deficiencies in ICI data in the following areas:

1. Hydrolysis
2. Photodegradation in water
3. Photodegradation on soil
4. Laboratory mobility studies
5. Field soil dissipation
6. Rotational crops (confined)
7. Fish accumulation

In response to these comments ICI submitted additional data to the Agency on January 15, 1987. The Agency in turn reviewed and provided comments on this resubmission to ICI on September 29, 1987. The Agency's comments indicated that deficiencies 1,2,3, and 5 above, were considered resolved. This review also noted that ICI had not submitted data to address anaerobic soil metabolism and reentry. Upon receipt of this review ICI requested a meeting with EAB to discuss the remaining deficiencies. The meeting was held on October 15, 1987.

Meeting Summary:

The outstanding data deficiencies listed in the most recent EAB review were addressed by ICI (see items A-E below). The discussion began with an explanation of the chemical relationship between PP321 and cyhalothrin. ICI emphasized

that cyhalothrin consists of four cis Z isomers only. PP321 consists of two cis Z isomers of cyhalothrin i.e. PP321 is one of the 2 pairs of enantiomers of cyhalothrin. (See page 1 of the attachment for chemical structures.)

A. Crop Rotation (Confined)

The EAB review states that additional data are needed on the uptake of the alcohol moiety of PP321 into rotated crops. Page 2 of the attachment was shown by ICI to establish that PP321 and cypermethrin contain a common alcohol moiety, 3-phenoxybenzyl cyanhydrin. ICI then referred to a confined crop rotation study on 14C-alcohol labelled cypermethrin which was previously submitted by ICI and accepted by EAB in support of the registration of cypermethrin. EPA had advised ICI in a May 1983 meeting that 14C-alcohol labelled cypermethrin studies would generally be acceptable to provide data on the fate of the alcohol moiety of PP321. Mr. Schlosser agreed to review and reconsider the arguments presented by ICI. Ms. Diveley stated that this deficiency appeared to be resolved, to which Mr. Schlosser agreed. [The data on cypermethrin was submitted and discussed in the October 1985 registration application for Karate.]

Mr. Schlosser asked about 14-CO2 levels subtracted from acid labelled PP321. ICI explained that control crop 14C-residues represent incorporation of 14-CO2 into the plants. Such incorporation is readily detectable for chemicals, such as PP321, which are readily degraded to CO2 in soil. Therefore it is appropriate to subtract the control values, i.e. 14-CO2 incorporation, from the values obtained for the treated plants. This explanation was previously presented to the Agency in the January 15, 1987 resubmission.

B. Anaerobic Soil Metabolism

ICI had reported and submitted this data in the same report with data on aerobic soil metabolism. Ms. Diveley indicated that the anaerobic study had not previously been reviewed by EAB due an oversight but was now being reviewed on an expedited basis. ICI emphasized that while this study used cyhalothrin as the test substance the study did track and account for both cyhalothrin and PP321 separately.

C. Fish Accumulation

ICI addressed the following EPA comments regarding this study.

1. The use of the term 'cyhalothrin' in this report is inconsistent.

This study was carried out in Japan to support USA and international regulatory requirements for cyhalothrin and

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PP321. The study report refers to all 16 isomers as 'cis, trans, Z, E, cyhalothrin', however the test substance used in the study was cyhalothrin which is isomer pairs A & B (the four cis, Z isomers).

2. The study used cyhalothrin rather than PP321.

In a May 1983 meeting EPA advised ICI that cyhalothrin data could be used to support registration for PP321. (A copy of the summary of this meeting is attached.) Consequently ICI carried out this study with cyhalothrin. It was explained that the fate of cyhalothrin and PP321 in both the environment and animals is very similar. It was also pointed out that EPA Toxicology Branch have decided to regulate cyhalothrin and PP321 as the same chemical for the purposes of establishing the ADI.

3. The data in the report was difficult to interpret and residue data was not tabulated.

This is an older study conceived and carried out in 1982/3 and reported in 1984. As such the data were presented in graphs only, however, individual data do exist to support the study.

4. The study used an inappropriate fish species.

It was pointed out that while this study used carp the EPA guidelines only specify that the "preferred" species is bluegill. Carp was chosen to satisfy both Japanese and USA registrations. ICI had previously used rainbow trout to study accumulation of cypermethrin which EAB had accepted. ICI therefore felt that carp, which is a USA species, should be equally acceptable.

5. The test substance specifications given in the report were inconsistent.

The test material was supplied by ICI to the contractor as cyhalothrin with an isomer A:B ratio of 61:39 with <2% trans isomer. The isomer A:B ratio in the test water was 53:47 with <5% trans isomer. It was reported that the isomer A:B ratio in test fish was 55:45 with <3% trans isomer present. The composition of the test substance was very similar in all three instances. In ICI's view however, it is the concentration of the test material in the test water that is of primary importance.

6. It is unclear why such a low nominal test substance concentration was used.

The EPA registration guidelines specify that the concentration should not exceed 1/10 of the 96 hour LC50 to the test species. For a flow-through test of this duration,

for a compound which can accumulate, ICI believe that toxic effects may be seen at this dose level. ICI, therefore, prefer to use 1/20 of the LC50 to avoid any fish toxicity. In a 72-hour static test carried out with cyhalothrin the LC50 to carp was 1.3 ug ai/liter and 1.1 ug ai/liter in a 96-hour replacement study. ICI believe this to be an underestimate of the true toxicity which is more likely 0.5 ug ai/liter and ICI prefer to use 1/20 of this value for fish accumulation testing. It was also pointed out that data for the pyrethroids permethrin, fenvalerate and flucythrinate indicate that water concentration does not significantly influence the BCF.

7. The characterization of the test water was inadequate.

ICI provided additional information on the characterization of the test water. The ratio of isomers A:B did not change significantly, ranging from 1:1 to 1:1.2 over the 28 days of the study. While the % of total 14C in water ranged from about 45% to 54% this lower amount actually results in a worse case calculation of the BCF. The ester hydrolysis products are of low toxicity to fish, they are polar compounds with low potential for accumulation in fish so it is of primary importance to monitor the parent A:B ratio which remained essentially constant throughout the study.

8. The concentrations of cyhalothrin in the treated water were variable.

Pyrethroids are lipophilic compounds which are strongly adsorbed to organic matter. Therefore it is extremely difficult to maintain constant concentrations in water due to the varying amounts of debris from fish. An examination of other pyrethroids shows that the cyhalothrin study data are within the range of variation seen with these other compounds. In fact a study with cypermethrin, which had more variation than the cyhalothrin study, was previously accepted by EAB. In any case the crucial information needed to calculate BCF is the concentration in the water and in the fish, both of which are known.

9. The study does not report data for the trans isomers in fish-tissue.

The trans isomers were not reported as the levels were so low as to be considered insignificant. Of the 0.05 ppm total residue in fish, <3% were trans isomers.

10. The types of plates used for TLC analyses were not reported. The limits of detection for the analytical methods used were not reported.

The TLC plate types are given on page 3 of the appendix to the report. Since data values were above the LOD's

and viewed as significant the actual LOD's were not given. The LOD's are available.

Calculation of BCF for PP321

The study report provides data on the concentration of cyhalothrin in the test water, the mean concentration being 5.9 ng/liter. The mean concentration of PP321 (isomer pair B) is 2.8 ng/liter. The total fish residues on day 28 of the study is given as 0.013 mg/kg PP321 (isomer pair B). Therefore the PP321 28-day BCF is 4600 for the total fish. The BCF derived similarly for cyhalothrin is 5100. Cyhalothrin and PP321 behave similarly, accumulating to a plateau and then depurating with half-lives of about 7 days, essentially the same as other pyrethroids.

D. Adsorption/Desorption (batch equilibrium)

ICI carried out this study to provide quantitative data on a range of soil types, in part to provide EPA with data that could be used in models.

Prior to carrying out this study ICI used accepted equations to predict the K_d of PP321 as approximately 2000. The solubility of PP321 in water is 0.004 ppm. If the initial solution concentration in a soil slurry was 0.004 ppm and the K_d is 2000, then at equilibrium, the solution concentration would be too low to allow accurate quantification. Therefore ICI chose to use initial solution concentrations which are 5 to 50x the water solubility of PP321. It was recognized however that it was vital that the concentration of ^{14}C -PP321 in the aqueous phases, at equilibrium, would not be constrained by the solubility of the compound. The actual concentrations of ^{14}C -PP321 were displayed to show that the vast majority of the solution concentrations were below 0.004 ppm. Although a few solution concentrations above 0.004 ppm were detected it is almost certain that this material was in solution during this test, the solubility of the test material being enhanced by the presence of both the co-solvent and dissolved soil organic matter. Both these factors would be expected to increase, considerably, the solubility of PP321 compared to that in pure water or buffer solutions.

EPA noted that there was some variability seen in the data, i.e. K_d values obtained from the replicates of the soil slurries were somewhat variable. ICI explained that this level of variability is inevitable in studies of this type and was probably due to the presence of minute amounts of particulate soil or soil organic matter in the equilibrium solutions even after vigorous centrifugation. Since the soil particles had an associated large radioactive residue, this would have had a profound effect on the measured solution concentrations and therefore on the derived K_d values.

EPA asked if a soil of less than 1% organic matter was tested. ICI indicated that 1.2% was the lowest organic matter content tested but this small difference would not make a real difference in terms of Kd.

Overall, ICI believes that this study is valid since the concentration of the test compound in the aqueous phases at equilibrium was not constrained by its water solubility. Further, very high Kd values were determined (1200 - 3200), indicating PP321 has an extremely low leaching potential. If these data are considered, together with the totality of the PP321 soil mobility data, ICI believes that there should be no concerns, whatever, concerning the possibility of leaching of either parent or degradates and therefore no further soil mobility studies should be necessary. ✓

E. Reentry

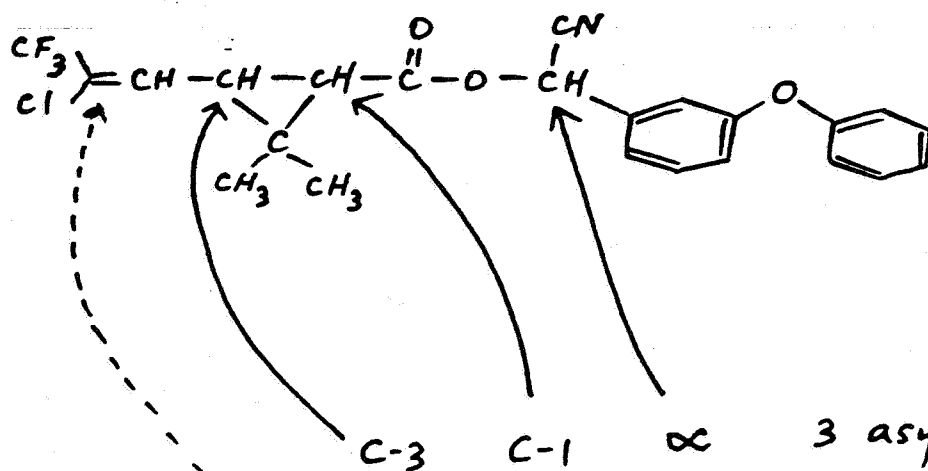
The EAB review indicates that reentry data are needed for this registration for cotton. It has been ICI's experience that cropping practices for cotton do not include reentry by farm workers therefore the need for this type of data is not triggered. This view is substantiated by the EPA registration of numerous pyrethroid compounds for cotton without such data.

Conclusion

Mr. Schlosser agreed that there were no other issues which ICI needed to address for registration of Karate for cotton. While Mr. Schlosser found the ICI responses generally reasonable and acceptable, he indicated that EAB would officially consider each of the arguments presented by ICI when they are officially submitted in writing.

JMW/10-19-87

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2 geometric isomers

Z- & E- isomers

3 asymmetric centers

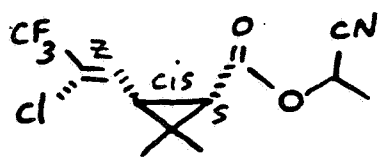
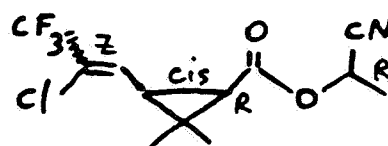
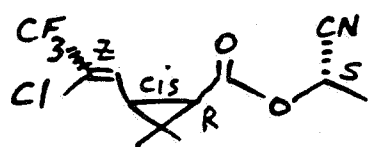
$2^3 = 8$ optical isomers

4 cis- &

4 trans- isomers

total 16 isomers theoretically possible

cyhalothrin consists of 4 cis Z isomers only



PP321 (pair B)

(pair A)

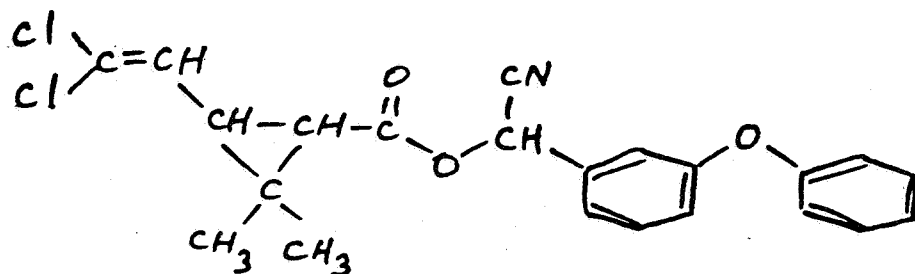
cyhalothrin

PP321 consists of 2 cis Z isomers only

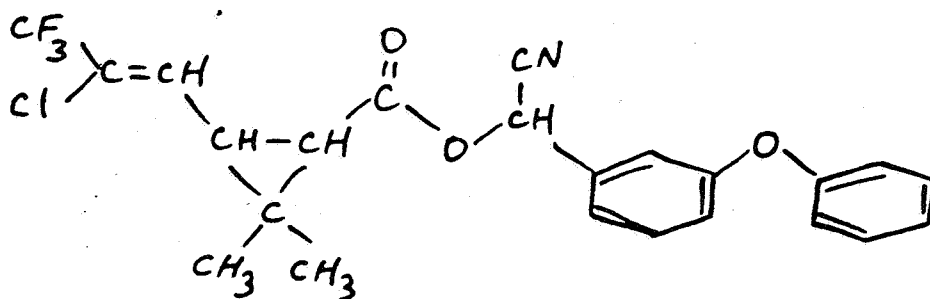
11

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ICI pyrethroid esters



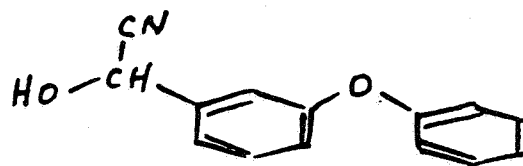
cypermethrin



cyhalothrin (x PP 321)

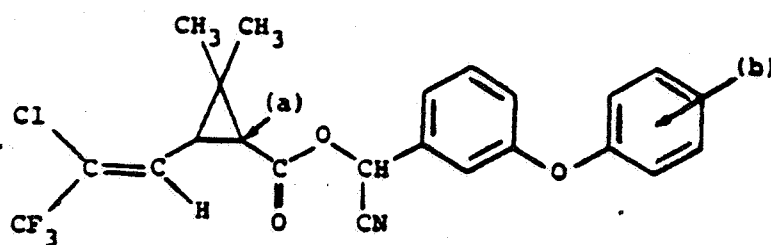
NOTE

Common alcohol



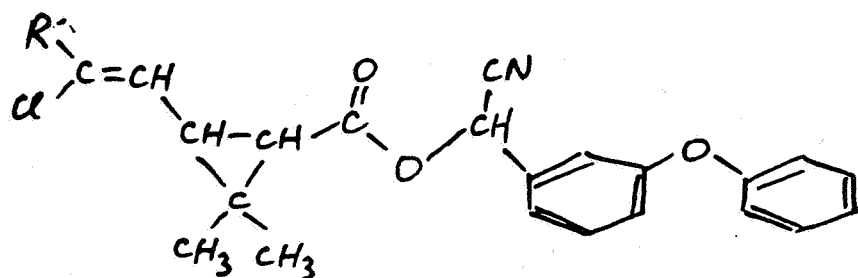
3-phenoxybenzyl cyanhydrin

FIGURE 1 : Position of Radiolabelling in ^{14}C -PP321 Samples



- (a) position of radiolabelling in ^{14}C -cyclopropane labelled PP321
- (b) position of radiolabelling in ^{14}C -[U]-phenyl labelled PP321

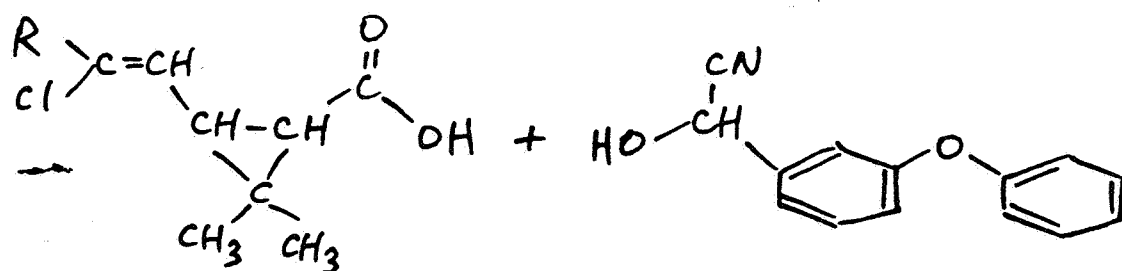
④



$R = Cl \equiv$ cypermethrin

$R = CF_3 \equiv$ cyhalothrin [PP321]

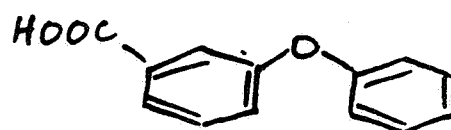
↓ ester cleavage



cyclopropane
carboxylic
acid

cyanhydrin

↓



3-phenoxybenzoic acid

May 18, 1983

Mr. Adam Heyward
Product Manager Team No. 17
Registration Division (TS-767C)
U.S. Environmental Protection Agency
Crystal Mall 2, Room 201
1921 Jefferson Davis Highway
Arlington, VA 22202

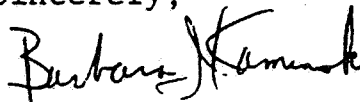
Dear Mr. Heyward:

RE: New Pyrethroids - PP321 and PP993
Pre-registration Conference

Thank you for arranging the pre-registration conference for PP321 and PP993 on May 9, 1983. The meeting was very productive and will enable ICI to more efficiently develop the data necessary to support PP321 and PP993 registrations. Please extend my appreciation to EEB and EAB staff for providing their valuable assistance.

I have enclosed a summary report of the meeting for your review and file. I believe you will find this document to be an accurate record of the decisions and conclusions reached at the conference. I would be grateful if you would circulate these minutes to the attendees from EAB and EEB and provide me with their comments on any items in the report.

Sincerely,



Barbara J. Kaminski
Senior Regulatory Coordinator

BJK/jgw
051683jgw08

cc: Mr. Timothy A. Gardner

Enclosure

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PP321 AND PP993 PRE-REGISTRATION CONFERENCE

NOTES OF A MEETING AT EPA ON MAY 9, 1983

Present:

Timothy Gardner - Registration Division - EPA

Adam Heyward - Registration Division - EPA

Dick Balcumb - Ecological Effects Branch - EPA

Wayne Faatz - Ecological Effects Branch - EPA

Richard Stephens - Ecological Effects Branch - EPA

Allan Vaughn - Ecological Effects Branch - EPA

Dick Moraski - Exposure Assessment Branch - EPA

Emil Regelman - Exposure Assessment Branch - EPA

Robert Hawk - ICI Americas Inc.

Barbara Kaminski - ICI Americas Inc.

Ian Hill - ICI PPD - Jealott's Hill

PP321 - POND STUDY

The Agency recommended that we request a waiver for this data requirement. To support our request we must demonstrate that PP321's behavior in the environment is sufficiently similar to permethrin and cypermethrin. The Agency would not accept a simulated pond study as a substitution for a field study.

Any pond study should include entry to the aquatic environment of the test chemical by drift and runoff. Furthermore, the Agency believes that pond studies should include an assessment of effects on productivity; for example, by monitoring planktonic species and algal populations.

PP321 - RADIOLABELING IN ENVIRONMENTAL HAZARD STUDIES

The Agency agreed it was reasonable to reference the data generated with cypermethrin to demonstrate the fate of the "alcohol half" (phenoxybenzyl moiety) of the molecule after ester cleavage.

The Agency also agreed that it was reasonable to reference isomer work done with cyhalothrin (PP563) provided the ratio of PP321 isomers present do not vary from those in cyhalothrin.

PP321 - BEE TOXICITY

The Agency agreed that the high toxicity values observed in laboratory tests with pyrethroids are not reflected under field conditions, but has not had time to review this area.

The Agency would like to see any of the data demonstrating the lack of effects of pyrethroids on bees in the field. Based on this review, the Agency believes we could avoid a field study; however, the bee toxicity warning on the label would have to be as stringent as that on the AMBUSH label.

PP993 - POND STUDY

The Agency does consider runoff a potential problem with a granular formulation. We can build a case for not doing further work by having PP993 data run through "SWARB", EPA's computer model that estimates runoff of granular formulations to rivers or ponds.

PP993 - FISH ACCUMULATION

The Agency prefers a flow-through study. They are not agreeable to a waiver in this area.

PP993 - TOXICITY TESTS ON MARINE FISH AND SHRIMP

The Agency suggested we write a letter to Clayton Bushong, Ecological Effects Branch Chief, concerning the need for toxicity work on marine species for a granular corn insecticide.

PP993 - BEE TOXICITY

The Agency does not require a foliar residue study, or a field study for a granular soil insecticide, even if it were shown to be highly toxic in the acute studies.

PP993 - RADIOLABELING IN ENVIRONMENTAL HAZARD STUDIES

The Agency agreed it was reasonable to reference the data generated with PP321 or cyhalothrin (PP563) to demonstrate the fate of the "acid" half (halovinylcyclopropane moiety) of the molecule after ester cleavage.

OTHER ISSUES

REPRODUCTION STUDIES ON AQUATIC SPECIES

EPA requires two reproduction studies, fish embryolarvae and aquatic invertebrate 'egg to egg'. The Agency noted that a Daphnia reproduction study would suffice most of the time for

the invertebrate study, even if the Mayfly or Mysid shrimp was shown to be the most sensitive species during the acute studies.

SUBSTANCE TO BE TESTED

The technical grade of the active ingredient need only be used for aquatic acute toxicity and reproductive studies.

FISH AND WILDLIFE REGISTRATION SUMMARY

The Agency would like a three or four page environmental fate summary to be included in the Fish and Wildlife summary. It should not be as in-depth as the discussion in the regular Section J.

REVIEW OF INDIVIDUAL STUDIES

The Ecological Effects Branch and the Environmental Assessment Branch expressed a willingness to review single studies as they become available to determine if they would satisfy data requirements.

051683jgw08/a