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

AUG 14 1992

MEMORANDUM

SUBJECT: Consideration of Conditional Registration for the New Microbial Bacillus thuringiensis Subspecies Aizawai for Terrestrial and Greenhouse Food and Non-Food and Stored Agricultural Commodity Uses (EPA File Symbols 275-IA and 275-IL)

- Decision Memorandum -

FROM: Anne E. Lindsay, Director
Registration Division

TO: Douglas D. Campt, Director
Office of Pesticide Programs

ISSUE

Should the Agency grant a conditional registration to the subject product which contains the new active ingredient B. thuringiensis subspecies aizawai under FIFRA section 3(c)(7)(C)?

BACKGROUND

Regulatory History

On July 26, 1991, Abbott Laboratories applied for registrations of the manufacturing-use product CenTari Technical Powder and the end-use product CenTari Water Dispersible Granule Biological Insecticide containing the active ingredient Bacillus thuringiensis subspecies aizawai. The CenTari trade name was subsequently changed to Xentari.

At the time of receipt, the Xentari applications were processed as new food use registrations of an already registered active ingredient. However upon consulting the Status of Pesticides In Reregistration and Special Review, put out by the Special Review and Reregistration Division in March 1992, Registration Division discovered that the single existing registration for Bacillus thuringiensis subspecies aizawai for use on empty honey combs against the greater wax moth larvae was canceled on January 22, 1991 due to nonpayment of maintenance fees. Thus, Abbot's Xentari products are now new active ingredients.

OPP Processing of the Application

On 4/17/92, HED completed their final review of these products and concluded that provided minor labeling changes regarding product storage were made that the toxicology and product analysis database was now complete. On 7/30/92, EFED completed their final review and indicated two studies were found supplementary and one was found invalid. On 6/23/92, BEAD concluded that registration of XenTari would be in the public interest. In a 6/29/92 letter, Abbott requested voluntary cancellation of these products on 1/15/94. RD mailed out the pre-acceptance letter on 8/6/92 and Abbott agreed on 8/7/92 to the conditions stated therein. Subsequent to the initial application, Abbott submitted additional information approximately 21 times.

Prior Experimental Use Permits

Experimental use permits were issued for each of the following crops for this product on 7/10/91: broccoli, cabbage, cauliflower, lettuce, minor crucifers/leafy vegetables, cotton, and alfalfa. All crops were tested except for alfalfa due to a time delay in the state EUP approval. Additional testing was approved for minor crucifers/leafy vegetables, broccoli, and cabbage on 3/10/92.

Correspondences Received Supporting the Registration of These Products

8/29/91 and 9/18/91 letters from the Lower Alabama Growers Association requesting Alabama to submit section 18s for CenTari and Alabama's response were included in the Public Interest Document.

On 10/25/91 the Florida Fruit and Vegetable Association submitted a letter to Anne Lindsay requesting registration of CenTari by the spring of 1992.

On 1/23/92 the Florida Watercress Growers wrote in support of CenTari. Stephanie Irene responded on 4/7/92 indicating that a registration could possibly be granted before June. **A letter informing the watercress growers of the use deletion is attached and will be sent upon issuance of the XenTari registrations.**

On 1/31/92 Long & Scott Farms, Inc. wrote a letter urging registration and reporting good efficacy.

On 2/10/92 Sanwa Growers, Inc. wrote to Anne Lindsay reporting good efficacy for CenTari and urging registration.

A 2/13/92 letter from Gary Leibee of the University of Florida supporting CenTari to Gary Tucker of the Florida Department of Agriculture was enclosed as part of the Public Interest Document.

On 2/19/92 Dr. Martha Roberts, Deputy Commissioner for Food Safety of Florida's Department of Agriculture and Consumer Services, wrote to Anne Lindsay requesting an expedited review of the CenTari applications.

On 9/25/91 Joseph White, Abbott's Director of Regulatory Affairs, wrote Douglas Campt concerning the status of the applications. Mr. Campt responded that barring any unforeseen circumstances that a registration decision should be completed sometime in May of 1992.

On 3/9/92 Joseph White wrote Mr. Campt regarding the registration status of CenTari. Phil Hutton, PM 18, responded on 7/8/92 indicating that barring any unforeseen circumstances a registration decision should be made before August.

USE SITES AND APPLICATION TIMING

Xentari WDG is for use on alfalfa; hay and other forage crops; berries and small fruit such as grapes, strawberries, and blackberries; bulb such as garlic and onions; cucurbits such as melons, cucumbers and squash; flowers, bedding plants and ornamentals all for ground application only; fruiting vegetables such as tomatoes, peppers and eggplant; greenhouse/shadehouse and other outdoor nursery crops such as leafy, herbs, brassica and fruiting groups; herbs, spices and mints such as basil chives, dill, leeks and peppermint; leafy and cole crops such as lettuce (head and leaf), kale, celery, spinach, broccoli, cabbage, mustard greens, brussel sprouts, cauliflower, collards, chinese cabbage, endive, kohlrabi, and parsley; legume vegetables such as beans, peas, lentils, and soybeans; root and tuber such as carrots, potatoes, beets and sugarbeets; stone fruit such as cherries, plum, peach, prune, and nectarine; pome fruit such as apples and pears; tree nuts such as almonds, pecan, walnut and filbert; pomegranates; small grains (ground use only); tropical fruits; asparagus; avocado; bananas, citrus, sweet and field corn; sorghum; cotton ; hops; kiwi fruit; malanga; peanuts; pineapple; rape; safflower; sunflowers (ground use only); tobacco; turf; watercress; forestry (ground application only); shade trees; sugar maple trees; ornamental trees; and stored agricultural products.

Applications may be repeated as necessary to provide control. 3 to 14 days is the recommended time between repeat applications.

TOXICOLOGY

The following studies were submitted and reviewed by the Agency.

Acute Intraperitoneal Study in the Mouse

Test Substance: Xentari Technical Powder

Dosing: 0.005, 0.05, 0.5 mg/animal which equates to approximately 1×10^5, 1×10^7 and 1×10^8 CFU/animal.

Results: No deaths or signs of toxicity were observed.

Subcutaneous Injection Study in the Mouse

Test Substance: Xentari Technical Powder

Dosing: 0.063 mg/animal which equates to approximately 1.35×10^8 CFU/ animal.

Results: No deaths or signs of toxicity were observed.

Acute Oral Toxicity/Pathogenicity Study in the Rat

Test Substance: Xentari WDG

Dosing: 1gm Xentari was diluted in 9ml sterile 0.1M phosphate buffer. 10ml of this suspension was then dosed at 10 ml/kg body weight or approximately 1000 mg Xentari WDG/kg body weight and 1.3 - 1.4 x 10^{11} CFU/animal.

Results: No mortality or significant treatment related clinical signs of toxicity were observed. The toxicity category based on the 1000mg/kg body weight dose is toxicity category III. Incomplete clearance due to possible degradation of the pesticidal microbe in the rat gut, reinfectivity, or the initial high dose was observed. However, since no deaths or significant clinical signs of toxicity were observed, HED did not foresee any unreasonable risk related to the use of the Xentari WDG.

Acute Intravenous Study in the Rat

Test Substance: Xentari Technical Powder

Dosing: 2.94 x 10^{7} CFU/ml applied at 3ml/kg body weight so at least 10^{7} CFU/ animal.

Results: No mortality or clinical signs of toxicity were observed in any of the animals. A pattern of clearance from the blood, cecum contents, liver, lungs, kidney, and brain was established. Viable organisms were found in the mesenteric lymph nodes and spleen at day 66, i.e. study termination. The numbers isolated, however, demonstrated a significant decline and the pattern of clearance observed is not unusual for Bacillus thuringiensis.

Acute Pulmonary Toxicity/Pathogenicity in the Rat

Test Substance: Xentari Technical Powder

Dosing: A single dose of 1.65 - 1.81 x 10^8 CFU/ animal.

Results: The test substance was non-toxic, non-infective, and cleared from the lungs within 3 days of administration. HED does not anticipate any unreasonable risk resulting from exposure via the pulmonary route.

Acute End-Use Product Toxicology Studies

Test Substance: Xentari WDG

Acute Dermal Toxicity : LD_{50} > 2,000 mg/kg, Toxicity Category III.

Acute Inhalation Toxicity : LC_{50} > 3.05 mg/L, Toxicity Category III.

Acute Eye Irritation : All irritation subsided by day 7, Toxicity Category III.

Acute Dermal Irritation : PII = 1.04, Toxicity Category IV.

Actual acute eye irritation, dermal toxicity and irritation, inhalation toxicity, and oral toxicity studies on the Xentari Technical were waived by HED/SACB since the components of the MP have been tested either in due course of fulfilling data requirements for the technical grade active ingredient or end-use product.

BT TOLERANCE EXEMPTION APPLICABILITY

HED/SACB concluded in their 11/12/91 review that the toxicological data submitted on the technical grade material supports including this product under the existing tolerance exemption for Bt (40 CFR 180.1011).

ECOLOGICAL EFFECTS

A series of nontarget organism studies were submitted to provide data on the XenTari Bacillus thuringiensis subspecies aizawai on nontarget birds, fish, aquatic invertebrates, honey bees and other beneficial insects. Although nontoxic to birds and fish; Xentari was highly toxic per os to adult honey bees, moderately to highly toxic to freshwater aquatic invertebrates, slightly toxic to green lacewings, and somewhat toxic to the predacious mite M. occidentalis.

A predatory wasp, Trichogramma pretiosum, study was submitted but found invalid due to unacceptable mortality in the controls. The rainbow trout study submitted was graded supplemental since it was done over a 96 hour period and not a 30 day period in which potential pathogenicity is evaluated as per Subdivision M. The Daphnia magna study was also found supplemental due to a lack of a sterile culture filtrate control and a lack of sufficient treatment concentrations necessary to determine an accurate EC_{50}.

The Agency needs additional data to determine the source of the unexpected activity against nontarget invertebrates, i.e. is the activity due to the spore-crystal complex or is it due to heat-labile or heat-tolerant exotoxins contaminating the XenTari technical material. If this toxicity is a characteristic of this particular Bt and not an artifact or contaminant, chronic toxicity/pathogenicity data will be required on honey bees, green lacewings, predatory mites, and Daphnia magna. The need for additional testing of Trichogramma pretiosum and rainbow trout will depend on the results of completed valid studies with these species.

SUMMARY OF DATA GAPS

The following studies are to be conditionally required in order to further assess the freshwater fish, Daphnia and predatory wasp hazard potential of XenTari as well as to determine the cause of observed toxicity in submitted studies.

Guideline Reference Number	Title of Study
154A-19	30 Day Freshwater Fish Toxicity/ Pathogenicity Testing

Guideline Reference Number	Title of Study
154A-23	Nontarget Arthropod Testing for Toxicity/Pathogenicity to Arthropod Predators/ Parasites for Trichogramma pretiosum
154A-20	Freshwater Aquatic Invertebrate Toxicity/ Pathogenicity Testing
N/A	Determination of the source of the unexpected activity against nontarget invertebrates, i.e. is the activity due to the spore-crystal complex or is it due to heat-labile or heat-tolerant exotoxins possibly contaminating the technical material.

LABELING

In order to minimize nontarget organism hazard, the following environmental hazard block is to be placed on the XenTari WDG label.

ENVIRONMENTAL HAZARDS

This product is toxic to aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwaters.

The toxicity of this product to the predatory wasp Trichogramma pretiosum is not known.

This product is toxic to the green lacewing and the predatory mite Metaseiulus occidentalis.

This product is highly toxic to honey bees exposed to direct treatment. Do not apply this product while bees are actively visiting the treatment area.

PUBLIC INTEREST FINDING

The data submitted in support of the conditional registration of XenTari appears to indicate that this product, when used in accordance with the label directions, can be as effective or more effective than the currently registered Bt products at controlling the diamond back moth and other lepidopterous pests. Based on the limited data, BEAD believes that XenTari, with its novel toxin mix, would be a useful addition to currently registered Bt products for control of resistant diamond back moth populations. Therefore, BEAD believes that, from a benefits perspective, conditional registration of Xentari would be in the public interest.

RECOMMENDATION

Although submitted data indicate acute toxicity against nontarget insects, including honey bees and aquatic invertebrates, these effects appear to be due to toxicity rather than pathogenicity.

The Registration Division recommends that XenTari WDG and XenTari Technical Powder containing Bacillus thuringiensis subspecies aizawai be conditionally registered under FIFRA section 3(c)(7)(C) with this conditional registration to expire on January 15, 1994.

Concur: _____

Nonconcur: _____

Date: AUG 17 1992

Attachments: Conditional Registration Letter
Supporting Correspondences
Letter to Water-cress Growers
Pre-Acceptance Letter
Voluntary Cancellation Letter
Scientific Reviews
Public Interest Finding