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

SEP 15 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Consideration of Conditional Registrations for the Use of the New Microbials Bacillus thuringiensis Subspecies kurstaki Strain EG2348 (Condor OF for Forestry Use) and Strain EA2371 (Cutlass OF and Cutlass WP for Vegetable Use)

FROM: Anne E. Lindsay, Director
Registration Division (H7509C)

TO: Douglas Campt, Director
Office of Pesticide Programs (H7501C)

Issue

Should the Agency grant a conditional registration to the subject single active ingredient products which contain the new active ingredient B. thuringiensis subspecies kurstaki strain EG2348 and strain EG2371 under FIFRA section 3(c)(7)(C)?

Background

On October 18, 1988, Ecogen, Incorporated (Ecogen) applied for the registration of the end-use product Condor OF containing the active ingredient Bacillus thuringiensis subspecies kurstaki strain EG2348 for the forestry use of controlling gypsy moth and spruce budworm. On December 22, 1988, Ecogen applied for registration of the end-use products Cutlass WP and Cutlass OF containing the active ingredient Bacillus thuringiensis subspecies kurstaki strain EG2371 for the food use of controlling lepidopteran insects on vegetables.

Prior to applying for registration, Ecogen obtained Agency approval to test these strains in small-scale field trials in 1986 and 1987. The pre-experimental use permit (EUP) approval was necessary since strains EG2348 and EG2371 were derived via plasmid curing and conjugation and these fall under the purview of the June 26, 1986 EPA policy for small-scale field testing of certain microbial pesticides (51 FR 23302). EUPs were obtained in 1988 for large-scale

field testing of strain EG2348 and EG2371. These EUPs were extended in 1989. The Cutlass EUPs were not crop destruct.

The inclusion of discussions regarding two new active ingredients and three new products is due to the large amount of data bridged between these products.

Regulatory Status

All required science support reviews for the section 3 registration have been completed. However, data gaps exist for toxicology, product chemistry, and nontarget organism studies.

Toxicology and Tolerance Exemption Status

Toxicology Data Base for Subject Ecogen Products

	Condor OF	Cutlass OF	Cutlass WP
Requirements			
For ai			
Acute Oral Tox/Path	NO	NO	YES
Acute Pulmonary Tox/Path	YES	NO	NO
Acute iv Tox/Path	YES	NO	NO
Mouse ip	YES	YES	YES
For EPs			
Acute Oral	NO	NO	NO
Acute Inhalation	NO	NO	NO
Eye Irritation	NO	NO	NO
Acute Dermal	NO	YES (II)	YES (IV)

Per Roy Sjoblad's August 16, 1989 review, data can be bridged between the Condor strain (EG2348) and the Cutlass strain (EG2371). Therefore, for the active ingredients no toxicology data gaps exist. In addition, since the inert ingredients and their percentages are identical to the Condor OF and the Cutlass OF products, the acute dermal study performed on the Cutlass OF satisfies this requirement for Condor OF.

On August 23, 1989, RD/IRB requested HED/SACB to give guidance concerning the toxicology data gaps for the subject three products. RD asked whether the remaining end-use toxicology studies were data gaps. HED responded that they were. RD also inquired whether protective clothing labeling would satisfy the requirements for acute eye and inhalation studies. HED responded by stating that the revised

Subdivision M does not require acute eye irritation studies on end-use products provided goggles are worn by mixer/loader/applicators. However, protective clothing labeling does not cancel the need for acute inhalation studies. RD also requested whether HED could extrapolate precautionary labeling for all routes of exposure based on the acceptable dermal studies. HED responded that such extrapolation was not possible. RD asked about the applicability of the 40 CFR 180.1011 tolerance exemption to the subject active ingredients. HED responded by stating that the tolerance exemption applied.

Product Chemistry

Existing Data Gaps for Cutlass WP, Cutlass OF, and Condor OF

Product Identity - 151A-10

- Standard biochemical testing according to Vol. 2 of Bergey's Manual of Systematic Bacteriology. Several laboratories may be contracted to perform such tests rapidly and economically.

- Standard Gram-positive antibiotic (including erythromycin) sensitivity testing.

- Although representatives of the insect orders Coleoptera, Hymenoptera, and Lepidoptera have been tested for their sensitivity to EG2371, a representative of each of the following orders must also be tested: Diptera, and Orthoptera.

- Although it is true that data reflecting subcutaneous injection of mice with each batch must be conducted (yet not submitted), such a study must be submitted on one representative batch as a condition of registration.

- Although the plasmid profiles for Condor are acceptable, a statement should be made as to which plasmids encode a toxin.

- Each crystalline endotoxin (inclusion) for Condor must be described in terms of morphology.

Analysis of Samples - 151A-13

- Although SACB agrees that spore counts need not appear on the label, the viable spore count of five commercial batches must be submitted as a practical range.

- The toxins in five commercial batches of Cutlass WP and the MP must be analyzed such that insect order bioactivity can be determined, e.g., % (w:w) lepidopteran-active toxin(s) or % (w:w) coleopteran-active toxin(s). The ingredient statement of the EP label must reflect this as noted on page 22 of the December 1988 Registration Standard.

Certification of Limits - 151A-15

- Certified upper and lower limits for each group of endotoxins distinguished by insect order affected. Validated methods to enforce such limits must be submitted.

Physical and Chemical Properties - 151A-16

- Storage stability data after storage of WP and MP for 1 year. The analytical method used to determine endotoxin should be specified. The b-endotoxin should be sought, quantified, and the method sensitivity stated. Also, any corrosion of containers, or lack thereof, should be noted.

Ecological Effects Data

A battery of studies were submitted and reviewed by the Ecological Effects Branch (EEB) in the evaluation of Condor™ OF, Cutlass OF™, and Cutlass WP™. Like the human health toxicology data, the nontarget organism data requirements utilized a large degree of data bridging. EEB determined that all nontarget testing performed on strain EG2348 (Condor) could be used to support strain EG2371 (Cutlass) except for nontarget insect testing. The Cutlass EEB review describes an EUP; however, verbal communication with the reviewer indicates that the conclusions hold true for the registration as well. For both the Condor and the Cutlass strains, risks to nontarget mammals, birds, plants and aquatic wildlife is minimal to nonexistent. Restrictive labeling for endangered species need not be instituted at this time, provided that the registration be conditional with the requirement that restrictive labeling must be implemented when such labeling is deemed necessary based on data received from the Registration Standard and/or further consultation with the U.S. Fish and Wildlife Service.

The risk of the Condor strain is minimal to nonexistent to nontarget insects. However, the parasitic hymenoptera study conducted on the Cutlass strain showed possible toxicity. EEB recommends that the study be rerun.

Ecological Effects Data Base for Subject Ecogen Products

Study	Strain Utilized In Testing	Finding
Avian Oral (Mallard)	EG2348	LD_{50} > 3.33 mg/kg body weight
Avian ip (Mallard	EG2101	LD_{50} = 188 mg/kg
Freshwater Fish (Rainbow Trout)	EG2348	No toxic or pathogenic signs observed
Aquatic Invertebrate (Daphnia magna)	EG2348	No toxic or pathogenic signs observed
Nontarget Plant Studies		
96-Hour Exposure	EG2101-OF	No adverse effects
Vegetative Vigor Test	EG2348-OF	EC_{50} = 61211 qt/A
Seed Germination/ Emergence	EG2348-OF	No adverse effects
Honey Bee	EG2348	No adverse effects
	EG2371	No adverse effects
Nontarget Beneficial Insect Studies		
Ladybug Beetles	EG2348	LD_{50} > 0.56 mg/beetle
	EG2371	LD_{50} > 0.56 mg/beetle
Parasite Hymenoptera	EG2348	LD_{50} > 0.56 mg/beetle
	EG2371	LD_{50} = 26%
Green Lacewing Larvae	EG2348	LD_{50} > 0.56 mg/beetle
	EG2371	No adverse effects

Public Interest Finding

Condor OF

The results from the efficacy documentation provided by the applicant are acceptable to support a public interest finding. Basically, the data indicate that Condor OF is slightly more efficacious than the registered Dipel 8L formulation. The submitted field trial data indicate that Condor OF is as effective as Dipel 8L with regard to egg mass reduction and life stage reductions. Condor OF provided significantly better foliar protection than Dipel 8L in the Ticehurst, PA studies and numerically better foliar protection in the second PA and DE/NJ studies. The Ticehurst 1987

bioassay results are intriguing because Condor provided a significantly longer residual than Dipel. If these results had been repeated in the field trials the difference between the two B.t. strains would be significant. The difference in the activity may have been due to fermentation/batch potency problems, application efficacy (deposition) or formulation problems. Regardless of the problem, the applicant should be able to duplicate these results in a subsequent bioassay and ideally in a field trial.

Cutlass OF

Registration of this product is in the public interest because it has been demonstrated to provide more effective control of resistant Diamondback Moth and subsequently reduce the amount of insecticides used on cruciferous crops to control this important pest.

Cutlass WP

Based on the data submitted, this product has not been shown to offer any advantages over currently registered B.t. based products. This product would be in the public interest if it is shown to provide superior control of resistant DBM. The DBM data that Ecogen submitted appeared to be conducted on a chemically susceptible population in Florida and results from the Weslaco, Texas field trial indicated that Cutlass WP provides control equal to Dipel 2XWP and endosulfan. It should be noted that this product contains the same strain as Cutlass OF, making control of resistant Diamondback Moth a realistic assumption. However, no data to support this contention have been submitted. This biological product certainly offers advantages over the currently registered chemical alternatives with respect to potential human and ecological hazards of the active ingredient.

Regulatory Rationale

With the exception of further testing needed on nontarget hymenoptera, the Ecogen products discussed in this memorandum have an extensive ecological effect data base. The toxicology data requirements for the active ingredients have been fulfilled and the Science Analysis and Coordination Branch of HED has concluded that the Bacillus thuringiensis tolerance exemption found in 40 CFR 180.1011 applies to the Cutlass food-use products.

Under the small-scale field testing of these genetically altered products in 1986 and 1987, several other government agencies reviewed these tests along with EPA. Per concurrence with the Science Integration and Policy Staff, RD

proceeded to treat the Ecogen EUPs via standard administrative procedures that non-biotech EUPs submitted to the Agency are treated.

On April 27, 1989, the Agency announced in the FEDERAL REGISTER that the active ingredients in the subject Ecogen applications for registration submitted to the Agency between October and December 1988 would be considered new active ingredients. The rationale for this decision was based on scientific deliberations and conclusions regarding B.t. strains during the development of the B.t. Registration Standard.

For the active ingredients, no toxicology data gaps exist. However, several data gaps exist for the product chemistry data requirements. However, these data gaps pertain mostly to enforcement issues and the B. t. Registration Standard identification requirements for B.t. strains.

With the exception of acute dermal studies, no acceptable toxicology studies for the end-use products are on file with the Agency. In Roy Sjoblad's September 14, 1989 memorandum to Herb Harrison, it was stated that the Agency does not have data on Condor OF, Cutlass OF, and Cutlass WP that would allow us to conclude that there would be no expected adverse adverse effects from acute oral and acute pulmonary exposure to the inert ingredients in any of the formulated products. Furthermore, there is no scientific basis for extrapolating precautionary labeling for all routes of exposure based on dermal irritation or toxicity data.

On September 13, 1989, Ecogen representatives met with Anne Lindsay, Herb Harrison, Harvey Warnick, and Mike Mendelsohn. The company discussed different aspects of the registration process for these products and stressed the great need for the company to obtain the Cutlass WP registration in order to survive. Steve Jellenick proposed labeling the products in a worst-case manner, referring to TOX II labeling. Herb Harrison responded that it was not Agency policy to overlabel a product.

Options for Consideration

1. Issue a conditional registration with a two year expiration date for all three products with the requirement that all data gaps, including those discussed for the end-use product, be filled and that the product be labeled TOX I for oral and pulmonary toxicity.

2. Deny registration of Condor OF and Cutlass OF (acute dermal irritation TOX II) at this time and request the outstanding data. Issue a conditional registration with a two year expiration date for Cutlass WP (acute dermal irritation TOX IV) with the requirement that all data gaps, including those discussed for the end-use product, be filled and that the product be labeled TOX I for oral and pulmonary toxicity.

3. Deny registrations at this time and request the outstanding data.

OPTION CHOSEN: option 1.

COMMENT: Need post mortem on issue of missing acutes on hymenoptera study.

DATE:

Attachment:

9/14/89 Sjoblad memorandum