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

AUG 2 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Consideration of Section 3(c)(7)(B) Conditional Amendment for Northrup King's *Bt* Corn Plant-pesticide: *Bacillus thuringiensis* CryIA(b) Delta-Endotoxin and the Genetic Material Necessary for It's Production in Corn (Plasmid Vector pZ01502) (EPA Registration No. 67979-E)

-DECISION MEMORANDUM-

FROM: Janet L. Andersen, Acting Director
Biopesticides and Pollution Prevention Division

TO: Daniel M. Barolo, Director
Office of Pesticide Programs

I. ISSUE

Should the Agency conditionally amend Northrup King's *Bt* corn product to expand the use of this plant-pesticide from limited plant propagation to full commercial use in field corn pursuant to FIFRA §3(c)(7)(B)?

The limitations currently placed upon the use of the active ingredient [which controls the European corn borer Ostrinia nubilalis (Huebner)] include but are not limited to the acreage which may be planted, the duration of the registration, geographic areas where the product may be used, and post-harvest agricultural practices.

II. SUMMARY AND REGULATORY BACKGROUND

A. Registration Applications

Northrup King has submitted an application which broadens the current use of their plant-pesticide registered for seed increase/hybrid production. This amendment would expand

the use of this plant-pesticide to include the full commercial use for field corn.

B. Tolerance Petitions

Monsanto Company submitted a petition (**PP 5F4473**) which requested that EPA establish an exemption from the requirement of a tolerance for residues of the plant-pesticide active ingredients *Bacillus thuringiensis* CryIA(b) delta-endotoxin and the genetic material necessary for its production in all plants. Approval of this petition eliminates the need to establish a maximum permissible level for residues of these plant-pesticides in all plant raw agricultural commodities.

Northrup King also submitted a petition for their specific active ingredient in corn. Since the Monsanto petition covers all forms of the CryIA(b) protein in all raw agricultural commodities, the Northrup King petition for their CryIA(b) protein is not discussed nor is there the need to establish a final rule for that petition.

Northrup King submitted a pesticide petition (**PP 5E4517**) which requested that EPA establish an exemption from the requirement of a tolerance for the plant-pesticide inert ingredient phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production (plasmid vector pZ01502) in corn. PAT confers resistance to the herbicide glufosinate-ammonium in the plant in which it is expressed.

C. Plant-pesticide Policy

The Agency published its proposed position on the regulation of pesticidal substances produced in plants (**59 FR 60496, November 23, 1994**). In the proposal, the Agency would designate the pesticidal substances produced by plants as plant-pesticides. In addition, the Agency issued proposed regulations that define certain categories of plant-pesticides that would be exempt from regulation under FIFRA and FFDCA. Plant-pesticides not exempt would be subject to regulation. The *Bacillus thuringiensis* delta-endotoxins are examples of plant-pesticides that would be regulated under the proposal.

On March 25, 1996, the Agency issued a registration limited in scope and duration that allowed Northrup King to produce field corn seed for seed increase and hybrid production only.

The Biopesticides and Pollution Prevention Division (BPPD), the Biological and Economic Analysis Division (BEAD), and the Pesticide Resistance Management Workgroup (PRMW) have evaluated the data submitted and/or cited by Northrup King. Based on these data and other relevant information, OPP believes that: 1) the applicant has submitted/cited satisfactory data pertaining to the proposed additional use, 2) the product will perform its intended function, and 3) the new use, as proposed by the registrant, would not significantly

2826

increase the risks of any unreasonable adverse effects to humans, nontarget organisms, or the environment from the food and feed use of this product in field corn. BPPD scientists have reviewed the information submitted with respect to health effects, and these data show that the product will be digested like any other protein and genetic material and will have no significant effects on human health. Likewise, the data submitted for ecological effects have identified no significant hazards to non-target organisms. The pesticide resistance management plan submitted by Northrup King has been reviewed. Certain terms and conditions were deemed necessary for these registrations in order to mitigate the risk of insect resistance to *Bacillus thuringiensis*.

The amended registration for food and feed use of this product in field corn, if granted, would be conditional under section 3(c)(7)(B) of FIFRA. The Agency is imposing terms and conditions as outlined in Section VI of this document to address resistance management concerns. The ecological effects data requirements imposed on the existing FIFRA § 3(c)(7)(C) registration for this plant-pesticide are still required.

These conditions and terms are being imposed to address concerns that insects will develop resistance to *Bt* plants and sprays which can be used on corn, cotton, and a variety of vegetable crops. The conditionally required data were not formally listed as a requirement for this active ingredient prior to the date of the submissions by Northrup King.

III. PUBLIC COMMENTS TO NOTICE OF RECEIPT

A. Comment in Response to Seed Increase and Full Commercial Use of this Plant Pesticide

The Agency received one comment opposing tolerance levels that were described by the commentor as being proposed in text attached to the end of her letter. The notice upon which comment was received did not give notice of filing or propose a tolerance level. Rather, it announced the receipt of applications to register new active ingredients including the *Bt* corn that is the subject of this Decision Memorandum.

The commentor raised the issue of potential roles of pesticides in neurotoxicity and supported "safe/safer" alternatives to toxic chemicals. The Agency believes that the subject active ingredient does not pose the risk of neurotoxicity. The data submitted and cited by Northrup King support the prediction that the CryIA(b) protein would be non-toxic to humans. When proteins are toxic, they are known to act via acute mechanisms and at very low dose levels [Sjobald, Roy D., et al. "Toxicological Considerations for Protein Components of Biological Pesticide Products," Regulatory Toxicology and Pharmacology 15, 3-9 (1992)]. Therefore, since no significant acute effects were observed, even at relatively high dose levels, the CryIA(b) delta-endotoxin is not considered acutely or chronically toxic.

For human health, this product falls into the category of "safe/safer" pesticides, as

supported by the response of the commentor.

B. General Comments in Response to *Bt* Corn

Several comments were received and addressed in the Ciba/Mycogen *Bt* corn decision document of August, 1995. The main concern expressed by commentors was that of insect resistance development. In addition, over 800 comments calling for the Agency to have "workable resistance management plans" before allowing further *Bt* plant-pesticide registrations have been received by the Agency. The Agency believes that the terms and limitations of this registration relative to resistance management adequately mitigate the risk of resistance developing during the duration of this conditional registration.

C. RESPONSE TO VAN DUYN LETTER REGARDING THE EFFECTS OF *Bt* CORN PRODUCING TOXIN IN THE SILKS AND KERNELS ON THE CEWS

On April 22, 1996 Dr. John Van Duyn, North Carolina Cooperative Extension Service, N.C. State University sent a letter to the Agency in regard to restricting the use of *Bt* corn in areas that also grow cotton (or vice-versa). He concludes that sales should not be restricted because there are adequate refugia provided by alternate crops and weeds that would be provide alternate hosts for European corn borer (ECB) and CEW (corn earworm, also known as the bollworm with the scientific name of Helicoverpa zea (Boddie)) other than just corn or cotton.

The letter from Dr. Van Duyn does not take into account the local and national negative impacts associated with registration of Northrup King *Bt*-corn in cotton states. Of importance is the concern that Northrup King *Bt* corn has expression in silks and kernels which will impact CEW.

The Agency has registered *Bt* cotton, *Bt* corn and *Bt* potato with an awareness that pesticide resistance management data are needed within three to five years following commercialization (first full year of commercial use was 1996) to fill gaps of knowledge. Where crop acreage implications are of such a large magnitude as for all the crops attacked by CEW, it is necessary to get the data before the decision is made to register *Bt* field corn in cotton growing states. Out of the 70 million acres of corn grown in the USA, there are about two million acres of corn grown in states producing most of the USA's 12 million acres of cotton.

The CEW only overwinters in the southern half of the USA. Resistance to *Bt* in the South will potentially cause the same resistance levels in the North because the moths with resistant genes would be carried along with susceptible CEW moths from the South each year by prevailing winds. That would limit the value of other uses of *Bt*, including foliar sprays against this insect over much of the USA.

Dr. Van Duyn's projections on percent of market share is not well grounded. His argument that a low market share for *Bt* crops as a reason to allow use of both *Bt* cotton and *Bt* corn in the same area are not well grounded. For example, some areas are already planting up to 96% *Bt* cotton within a year of registration. It is also likely that there will be many more registrants with this new technology in the near future.

It is likely that there is a large disparity in potential cotton losses over field corn loses in the South if bollworm (CEW) develops resistance to *Bt*. The current *Bt* cotton does not have a "high" dose control titer against the CEW/bollworm as it does against the tobacco budworm. This makes the bollworm conducive to selection for *Bt* resistance. *Bt* corn appears to be even less effective against H. zea, portending additional selection and a potential resistance problem in a foreseeable short time.

The Agency needs more data before it can make an informed decision on the registration of corn expressing *Bt* toxins in the kernels and silk in the South. When a variety of *Bt* genes, other gene technology and pyramiding of genes are registered, the Agency will be better able to evaluate resistance management strategies for crop and pest complexes such as H. zea and the many crops it attacks.

IV. SCIENCE ASSESSMENT

The discussion that follows summarizes BPPD's reviews of the data available to the Agency on these plant-pesticide active ingredient. A more detailed discussion of this assessment is provided in the Data Evaluation Records for the studies summarized below.

A. Human Health

1. Product Identity

The new active ingredient has been identified as *Bacillus thuringiensis* CryIA(b) Delta-Endotoxin and the Genetic Material Necessary For It's Production (Plasmid Vector pZ01502) in Corn. The registrant, Northrup King, refers to this product as its *Bt* 11 Corn Line.

Northrup King's corn line *Bt* 11 was produced by transforming another proprietary corn line with plasmid PZO1502 which contains genes for a truncated CryIA(b), PAT and AMP^r. The *cryIA(b)* gene was also altered to improve its GC ratio for expression in corn. The AMP^r gene was removed and is not present within Northrup King's *Bt* 11 corn line.

2. Product Analysis

a. CryIA(b)

Data were presented which showed that the truncated *CryIA(b)* toxin can be extracted from corn leaf tissue and this purified material displays characteristics and activities similar to that produced in *E. coli* which has been transformed to produce *CryIA(b)*. The similarities are shown for the tryptic core proteins in molecular weight after SDS-PAGE, immunorecognition in Western blots and ELISA, partial amino acid sequence analysis, lack of glycosylation and bioactivity against either European corn borer or corn earworm. This analysis justifies the use of the microbially produced toxin as an analogue for the plant produced protein in mammalian toxicity testing.

b. Phosphinothricin Acetyltransferase (PAT)

PAT confers resistance to the herbicide glufosinate-ammonium. PAT was shown to be readily inactivated by heat or mild acidic conditions and readily degraded in an *in vitro* digestibility assay. The *in vitro* digestibility studies indicate that the PAT enzyme would be rapidly degraded following ingestion.

3. Toxicology Assessment

a. Toxicity

The toxicology data provided are sufficient to demonstrate that there are no foreseeable human health hazards likely to arise from the full commercial use of the plant-pesticide active and inert ingredient corn line *Bt* 11. In addition, the Agency believes proteins shown to be equivalent to CryIA(b) by structural homology could also be found to pose no foreseeable human health hazards.

The data submitted regarding potential health effects of CryIA(b) and PAT include information on the characterization of the expressed proteins in corn, the acute oral toxicity of CryIA(b), a comparison of the amino acid sequence of the PAT protein to known mammalian toxins, and *in vitro* digestibility studies of these proteins. The acute oral toxicity test of bacterially-derived CryIA(b) protein showed no test substance related deaths at a dose of 4000 mg/kg.

The acute oral toxicity data submitted support the prediction that the CryIA(b) would be non-toxic to humans. When proteins are toxic, they are known to act via acute mechanisms and at very low dose levels [Sjobald, Roy D., *et al.* "Toxicological Considerations for Protein Components of Biological Pesticide Products," Regulatory Toxicology and Pharmacology 15, 3-9 (1992)]. Therefore, since no significant acute effects were observed, even at relatively high dose levels, the CryIA(b) delta-endotoxin are not considered acutely toxic.

Adequate information was submitted to show that the CryIA(b) test materials derived from microbial cultures were similar to the proteins produced by the plant-pesticide ingredients in corn using biochemical characteristics and bioassays against susceptible insects. Production

of microbially produced protein was chosen in order to obtain sufficient material for testing. In addition, the *in vitro* digestibility studies indicate the proteins would be rapidly degraded following ingestion.

Regarding the PAT protein, the Agency expects proteins with no significant amino acid homology to known mammalian protein toxins, which are readily inactivated by heat or mild acidic conditions and readily degraded in an *in vitro* digestibility assay to have little likelihood for displaying oral toxicity. The *in vitro* digestibility studies indicate that the PAT enzyme would be rapidly degraded following ingestion. Further, the PAT enzyme was shown to have no significant amino acid homology to known mammalian protein toxins.

The genetic material necessary for the production of the plant-pesticide active and inert ingredients are the nucleic acids (DNA) which comprise (1) genetic material encoding these proteins and (2) their regulatory regions. "Regulatory regions" are the genetic material that control the expression of the genetic material encoding the proteins, such as promoters, terminators, and enhances. DNA is common to all forms of plant and animal life and the Agency knows of no instance where these nucleic acids have been associated with toxic effects related to their consumption. These ubiquitous nucleic acids as they appear in the subject active ingredient have been adequately characterized by the applicant. Therefore, no mammalian toxicity is anticipated from dietary exposure to the genetic material necessary for the production of the subject active and inert plant pesticidal ingredients.

b. Allergenicity

Current scientific knowledge suggests that common food allergens tend to be resistant to degradation by heat, acid, and proteases, are glycosylated and present at high concentrations in the food.

Data has been submitted which demonstrates that the CryIA(b) delta-endotoxin is rapidly degraded by gastric fluid *in vitro* and is non-glycosylated. Similarly, the PAT protein is rapidly degraded in the gastric environment.

Studies submitted to EPA done in laboratory animals have not indicated any potential for allergic reactions to *B. thuringiensis* or its components, including the delta-endotoxin in the crystal protein. Despite decades of widespread use of *Bacillus thuringiensis* as a pesticide (it has been registered since 1961), there have been no confirmed reports of immediate or delayed allergic reactions to the delta-endotoxin itself despite significant oral, dermal and inhalation exposure to the microbial product. Several reports under FIFRA § 6(a)2 have been made for various *Bacillus thuringiensis* products claiming allergic reactions. However, the Agency determined these reactions were not due to *Bacillus thuringiensis* itself or any of the cry toxins.

Thus, the potential for CryIA(b) and PAT proteins to be food allergens is minimal.

4. Residue Chemistry

Residue chemistry data were not required for the subject plant-pesticide ingredients because of the lack and predicted lack of mammalian toxicity. This is similar to the Agency position regarding toxicity and the requirement of residue data for the microbial *Bacillus thuringiensis* products from which this plant-pesticide was derived. [See 40 CFR Sec. 158.740(b).] For microbial products, further toxicity testing to verify the observed effects and clarify the source of the effects (Tiers II & III) and residue data are triggered by significant acute effects in studies such as the mouse oral toxicity study.

a. Tolerance Exemption Conclusions

Based on the information considered, the Agency has concluded that establishment of tolerances are not necessary to protect the public health. Therefore, the exemptions from tolerance have been established as set forth below.

1) *Bacillus thuringiensis* CryIA(b) delta-endotoxin and the genetic material necessary for its production all plants.

Bacillus thuringiensis CryIA(b) delta-endotoxin and the genetic material necessary for its production in all plants are exempt from the requirement of a tolerance when used as plant-pesticides in all plant raw agricultural commodities. "Genetic material necessary for its production" means the genetic material which comprise (1) genetic material encoding the CryIA(b) delta-endotoxin and (2) its regulatory regions. "Regulatory regions" are the genetic material that control the expression of the genetic material encoding the CryIA(b) delta-endotoxin, such as promoters, terminators, and enhances.

2) Phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production (plasmid vector pZ01502) in corn.

Phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production (plasmid vector pZ01502) in corn is exempt from the requirement of a tolerance when used as a plant-pesticide inert ingredient in all raw agricultural commodities of field corn, sweet corn, and popcorn. "Genetic material necessary for its production" means the genetic material which comprise (1) genetic material encoding the phosphinothricin acetyltransferase and (2) its regulatory regions. "Regulatory regions" are the genetic material that control the expression of the genetic material encoding the phosphinothricin acetyltransferase, such as promoters, terminators, and enhances.

B. Gene Flow Potential

1. Potential for Outcrossing and Weediness

Although corn is thought to have evolved from a wild weedy species, corn today cannot exist in the wild as a weed because the female inflorescence, or the ear, restricts seed dispersal. Corn is an open pollinating (cross-fertilizing) species, probably descended from teosinte, which is more weedy, has more tillers, and does not have ears, as such.

2. Potential for Outcrossing with Wild Corn Species

a. *Teosinte*

Like corn, teosinte also has 10 chromosomes, is wind (open) pollinated, and tends to outcross, but is a highly variable species genetically compatible and interfertile with corn. Corn and compatible species of teosinte freely hybridize when in proximity to each other. In Mexico and Guatemala, teosinte exists as a weed around the margins of corn fields. A frequency of one F1 hybrid (corn x teosinte) for every 500 corn plants, or 2-5% of the teosinte population, has been reported. The F1 hybrid is robust, fertile, and capable of backcrossing to corn. However, except for special plantings, teosinte is not present in the U.S. Its natural distribution is limited to Mexico, and Guatemala.

b. *Tripsacum*

Tripsacum/corn hybrids have not been observed in the field, but have been accomplished in the laboratory using special techniques under highly controlled conditions. The risk of *Tripsacum*/corn hybrids in the field is considered minimal. Tripsacum/teosinte hybrids have not been able to be produced. Tripsacum species are perennials and seem more closely related to the genus *Manisurus* than either corn or teosinte. *Tripsacum*/corn offspring, when they occur, display various levels of sterility. Of the 16 species of *Tripsacum* described, one is native to the
southern tip of Florida, 12 are native to Mexico and Guatemala, and 3 are native to South America.

3. Potential for Outcrossing with Cultivated Zea Varieties

Corn pollen has been shown to travel up to 2 miles under favorable wind conditions. All corns will interpollinate except for certain popcorn varieties. Corn pollen germinates almost immediately after pollination and completes fertilization within 24 hours. Thus corn pollen is highly promiscuous and certification standards for distances between different corn genotypes have been established to maintain desired levels of purity in the production of hybrid corn (a minimum of 660 feet).

4. Weediness of Corn

Transformation causes no change in a corn plant's inability to exist as a weed. Likewise, the ability to outcross with teosinte and tripsacum (under carefully controlled conditions) will not be changed. Since both teosinte and tripsacum are included in botanical gardens in the U.S., the possibility exists (although unlikely) that exchange of genes could occur between corn and its wild relatives. However, no such case has been known or reported in the U.S.

Gene exchange between cultivated corn and transformed corn would be similar to what naturally occurs at the present time within cultivated corn. Plant architecture and reproductive capacity of the intercrossed plants will be similar to normal corn, and the chance that a weedy type of corn will result from outcrossing with cultivated corn is extremely remote.

C. Environmental Fate

1. Laboratory Degradation Study

B.t.k. CryIA(b) protein bioactivity, added to the soil as a component of corn line #754-10-1 tissue decreased with an estimated half life of 1.6 days and an estimated DT_{90} of 15 days. CryIA(b) protein bioactivity of corn line #754-10-1 tissue incubated without soil decreased with an estimated half life of 25.6 days, and a DT_{90} of 40.7 days. The bioactivity of purified CryIA(b) protein in soil decreased with an estimated half life of 8.3 days and a DT_{90} of 32.5 days.

2. Northrup King *Bt* 11

B.t.k. protein is expressed throughout the corn plant, but is concentrated in the leaves, where concentrations range from 10-168 ng B.t.k. protein/mg total plant protein (uncorrected for extraction efficiency). Levels of B.t.k. protein decrease as the plant reaches full maturity and begins to senescence. However, near the time of full maturity, the silk and kernels still contained 6.6 and 8.2 ng/mg, respectively. These residual levels may play a role in corn earworm resistance selection.

Estimated total B.t.k. protein per acre of corn is 0.57 pounds based on a total biomass of 89,300 pounds at physiological maturity (approximately 55-65 days after silking). The highest concentrations are in the leaf at approximately 3.3 ug/g fresh weight.

B.t.k. protein degrades in soil over time (1-3 weeks), apparently at a faster rate than total plant protein. After one week, approximately 1% and 10% of the original levels of B.t.k.
protein remained in leaf and stalk tissue, respectively. After three weeks, B.t.k. protein was still detected in the stalk tissue, but the level in transgenic leaves was similar to the background levels seen in control leaf tissue. B.t.k. protein apparently binds to soil particles, making quantitative extraction difficult.

Biological activity, assessed by European corn borer bioassay, is reduced to control levels after three weeks of incubation in soil.

D. Ecological Effects

1. Background

Acceptable studies have been submitted which demonstrate that *E. coli*-derived, purified B.t.k. CryIA(b) toxin has minimal adverse impact on the honey bee, and other non-target insects (parasitic hymenopteran, green lacewing, and lady bird beetles), and soil organisms (earthworm). Quail and catfish studies were generated using CryIA(b) containing kernels. Additional data is needed to more fully characterize the risk to Collembola and aquatic invertebrates. However, the overall risk to populations of these organisms is anticipated by the Agency to be minimal during the duration of this conditional registration.

2. Impacts on Non-Target Organisms

a. Levels of Exposure

B.t.k. protein is most highly expressed in the leaf tissue, in the order of 3.3 ug/g fresh weight (3.3 ppm) at physiological maturity. Field corn varieties can take from about 90 to 125 days to maturity. Peak expression in the leaf occurs at around 25 days after planting at approximately 168 ng/mg plant protein (168 ppm) (uncorrected for extraction efficiency). At 84 days after planting, levels in the leaf drop to 10.2 ng/mg (10.2 ppm). At maturity, leaf tissue averages 3.3 ug/g fresh weight (3.3 ppm). Levels in other tissues at maturity range from 0.4 ppm in the kernel to 16.2 ppm in the cob, with most tissues averaging approximately 6 ppm.

b. Impacts on Non-Target Insect - Honey Bee (Larvae)

B.t.k. HD-1 protein at 20 ppm is practically non-toxic to larval honey bees. An LC_{50} was not possible to calculate since this was a single dose test. Therefore, the NOEL is greater than 20ppm.

c. Impacts on Non-Target Insect - Honey Bee (Adult)

There were no statistically significant differences among the various treatment and control groups due to the sizable mortality that occurred in all treatments. B.t.k. HD-1 protein at 20 ppm resulted in a mean mortality of 16.2%. Because mortality was observed at the single dose tested, a NOEL could not be determined from this study, but it was less than 20 ppm. 20 ppm was determined to be significantly higher than exposure conditions in the environment.

d. Impacts on Non-Target Insect - Parasitic Hymenopteran

B.t.k. HD-1 protein at 20 ppm is practically non-toxic to *Brachymeria intermedia*. Since this is a single dose study, an LC_{50} cannot be calculated. The NOEL is greater than 20ppm.

e. Impacts on Non-target Insect - Green Lacewing Larvae

B.t.k. HD-1 protein at 16.7 ppm is practically non-toxic to green lacewing larvae after 7 days. The NOEL is greater than 16.7 ppm.

f. Impacts on Nontarget Insect - Lady Beetles

B.t.k. HD-1 protein at 20 ppm is practically non-toxic to lady beetles such as *Hippodamia convergens*. The NOEL is greater than 20 ppm.

g. Impacts on Birds - Northern Bobwhite Quail

No treatment related mortality or differences in food consumption, body weight or behavior occurred in birds fed 50,000 or 100,000 ppm transgenic corn meal derived from Monsanto's MON 80187 corn line (which contains CryIA(b) protein) relative to birds fed corn meal made from parental corn lines which did not express *Bt* toxin. Although this study utilized Monsanto's *Bt* corn for testing, the test material was considered sufficiently similar to the Northrup King corn grain to bridge the data.

h. Impacts on Earthworm

The 14-Day LC_{50} value for earthworms exposed to CryIA(b) insecticidal protein derived from *E. coli* in an artificial soil substrate was determined to be greater than 200 mg/kg (ppm), which was the single concentration tested. There were no statistically significant effects at the single dose tested. Therefore the NOEL is greater than 200 ppm. Although this study was graded supplemental, *Bt* toxins expressed in the corn plant are not expected to generate a toxic effect in the earthworm; therefore, no additional follow-up of this study is required.

i. Impacts on Collembola

Impacts on non-target soil organisms are of concern because of the residual B.t.k. protein that exists in the corn plant at physiological maturity and the concomitant potential for incorporation into the soil. Northrup King has cited a study assessing impacts on Collembola spp., which has been rated as a "supplemental" study due to the form of the test material. The Agency asked for a Collembola study using lyophilized leaf extract as the test material subsequent to the initial registration application, but, to date, the registrant has only cited one using purified CryIA(b) toxin derived from *E. coli* as the test substance. Therefore, Northrup

18976

King must fulfill this unfulfilled data requirement and submit or cite the required Collembola study.

In the study cited by Northrup King, purified B.t.k. insecticidal proteins derived from *E. coli* (200 ppm), including CryIA(b) toxin, had no observable toxicological effect on two species of Collembola: *Folsomia candida* and *Xenylla grisea*. The applicant has been informed via Agency letter that this study does not adequately addresses the Agency's non-target soil organism concerns because it was conducted with purified *E. coli*-produced B.t.k. protein and not lyophilized leaf extract, as the Agency requested. The rationale for the required study is that there is another study on file that demonstrates toxicity to Collembola, using lyophilized leaf extract as the test material, while control leaf extract did not. Northrup King has contended that plant extracts cannot be tested because they contain numerous allelochemicals that are potentially toxic to Collembola and would, thus, confound the results. However, the other Collembola study did not show effects with the control leaf extract. EPA requires a study which will include control plant extracts from non-transgenic parental corn lines and plant extracts containing Northrup King's *Bt* plant-pesticide.

j. Impacts on Channel Catfish

The study "Evaluation of the European Corn Borer Resistant Corn Line MON 801 as a Feed Ingredient for Catfish" was reviewed to determine potential impacts on channel catfish from Northrup King's *Bt* 11 corn line. Feed per fish, feed conversion ratios, final weight, percentage weight gain and survival were not significantly different between fish fed the control MON 800 diet when compared to those fed the diet containing transgenic corn from the test line MON 801. Body composition data exhibited no significant differences in percentage moisture, fat, or ash, with a higher protein content in the test fish on a dry weight basis. This difference in protein content disappears when one expresses the results on a wet weight basis. Data in this study are consistent with historical controls for catfish grown at the Delta Research and Extension Center.

Although this study utilized Monsanto's *Bt* corn for testing, the test material was considered sufficiently similar to the Northrup King corn grain to bridge the data.

k. Impacts on Aquatic Invertebrates

Northrup King did not submit or cite a toxicity study for *Daphnia magna*. Northrup King presented a rationale for a waiver of the daphnid studies, citing low exposure potential and lack of effects posed by products already on the market. The major source of B.t.k. protein in fresh water would be corn pollen, which has been shown to have expression levels of approximately 0.125 ug/g fresh weight, assuming pollen to be 10% protein by weight (0.30 ppm). The registrant argues that low exposure levels and lack of observed toxicity to a large number of aquatic invertebrates is adequate basis for a waiver. Further, Northrup King's statements in their waiver request regarding lack of demonstrated toxicity to aquatic

13876

invertebrates by *Bt* commercial products already on the market is inaccurate. Several studies on file with the Agency demonstrate adverse effects on daphnids. Due to the potential exposure of aquatic invertebrates to corn pollen containing the B.t. CryIA(b) toxin, this requirement will need to be addressed by the applicant by conducting a *Daphnia magna* study.

1. Impacts on Mammals

Both the scientific literature and the acute oral mouse study results indicate that no toxicity is expected in mammals. Therefore, no further testing on mammals in indicated.

3. Impacts on Endangered Species

A Biological Opinion was issued on December 18, 1986, concerning the possible effect of foliar spray of *Bacillus thuringiensis* subsp. *kurstaki* (*Bt*) on threatened and endangered species. Based on the difference in exposure scenarios between foliar *Bt* spray and *Bt* delta endotoxin expressed in corn plants, EPA believes that the Biological Opinion is not applicable and that reinitiation of consultation is not required.

The primary route of exposure to foliar *Bt* sprays is through either direct application to the crop or as a result of drift from spray or aerial applications.

In comparison, the primary route of exposure to *Bt* delta endotoxin in corn is through ingestion of corn tissue. There are no reports of threatened or endangered species feeding on corn plants, thus such species would not be exposed to corn tissue containing the CryIA(b) delta-endotoxin. Corn is widely grown, and above ground feeding damage is easily observed on corn plants due to its morphology and the way it is grown. Consequently, the identities of organisms that feed on corn are well established.

Another possible route of exposure is from corn pollen containing the delta-endotoxin that can drift from corn fields. As discussed previously in this section, the applicant has submitted adequate data for representative species to substantiate that the delta-endotoxin is practically nontoxic. The applicant did not submit or cite sufficient toxicity data for Collembola and failed to submit a toxicity study for *Daphnia magna*. There are no threatened or endangered soil invertebrates that are closely related to Collembola. Similarly, there are no threatened or endangered arthropods that are closely related to the *Daphnia manga*.

In addition, EPA does not expect that any threatened or endangered species will be affected by exposure to the delta-endotoxin via weediness or outcrossing to wild relatives or by competition with such entities. Hybrid corn, such as the corn that contains the pesticide at issue here, cannot exist in the wild nor are there wild relatives that can interbreed with corn in the United States. See section B above for a more detailed discussion of the potential for weediness and outcrossing to wild relatives.

14726

Because EPA expects that threatened or endangered Lepidopteran insects and other species will not be exposed to the *Bt* delta endotoxin, and because the most probable exposure scenario does not appear to affect listed species, EPA believes that this action will have no effect on any threatened or endangered species.

E. Resistance Management

Northrup King has submitted a resistance management plan. With this plan there are two major resistance concerns for the primary target pest, ECB, and a secondary pest, corn earworm (CEW)/ bollworm [*Helicoverpa zea* (Boddie)] . Northrup King's *Bt* corn is different from the previously registered *Bt* corn products because they express the CryIA(b) delta-endotoxin in silks and kernels. CEW prefer to feed upon silks and kernels, although they also feed upon the whorl. The CEW can also migrate long distances, can move from corn to cotton, and will move from the South to the North on prevailing winds as the season progresses. Therefore, the Agency believes that there will be substantial additional selection pressure for resistant CEW by Northrup King's *Bt* corn than there is for existing *Bt* corn products. Additional mitigation measures are recommended to limit the selection pressure for CEW resistance especially in the southern U.S. where cotton production states and cotton growing areas are or could be in close proximity to Northrup King's *Bt* corn. These measures will be discussed more fully below.

1. General Conclusions

Northrup King 's plan has addressed all of the general elements of a resistance management program, some only superficially. These elements include pest biology, *Bt* dose deployment, refugia, monitoring for ECB resistance, susceptible nontarget Lepidoptera pests, cross-resistance, IPM fit, grower education and communication, and development of alternative pesticides with different modes of action.

Based on an analysis of all of the available information submitted by Northrup King, the Agency concludes that the submitted resistance management plan has the necessary workable elements, but additional data must be collected to provide a solid basis for a long-term resistance management plan. Research should be performed, data collected, and modifications to the plan should be implemented within approximately two to four years following the date of this registration.

The submitted resistance management plan should adequately manage lepidopteran resistance to the CryI delta-endotoxins produced in field corn in the first 2 to 4 years following commercialization except for cotton production states and cotton growing areas in border states where the selection pressure for the development of CEW resistance will be considerably higher. The effectiveness of the current plan is mainly based upon the unlikelihood that these hybrids will dominate the market during this period.

The original estimate by the Agency for a resistance management plan was 3 to 5 years after commercial use. However, *Bt* corn has already been registered and grown commercially in 1996. As long as all commercial seed corn production is not immediately switched on a local or national level to corn producing CryI delta-endotoxins, unstructured or market-driven refugia should be adequate for approximately 2 to 4 years following initial commercialization because there will be natural refugia between fields (spatial mosaics). Because of the larval mobility and availability of alternate hosts, within-field seed mixes are not likely to be an effective refugia. Therefore, structured refugia where there are blocks of *Bt* plant-pesticide corn and conventional corn or other host plants will be necessary.

Market projections indicate that such market-driven unstructured refugia should exist during this initial commercialization period except in cotton production areas. However, after this initial period of CryI corn introduction, structured refugia will be necessary to ensure the success of the proposed resistance management strategy. Therefore, the resistance management strategy will likely be unworkable after two to four years following initial commercialization without structured refugia.

The Agency is concerned about the ramifications of corn earworm (CEW)/ bollworm resistance developing in insect populations that feed on both corn and cotton along with the development of ECB resistance. CEW will be suppressed by ECB-protected corn as it is in *Bt* cotton. However, the level of suppression is not really known. CEW resistance could negatively affect the utility of *Bt* cotton, and *Bt* foliar sprays on vegetables and other crops.

There is a potential for CEW resistance developing in both corn and cotton. Northrup King's *Bt* corn is different from the previously registered *Bt* corn products because it expresses the CryIA(b) delta-endotoxin in silks and kernels. CEW prefer to feed upon silks and kernels, although they also will feed in the whorl early in the season. Therefore, the Agency believes that there will be substantial additional selection pressure for resistant CEW than there is for existing *Bt* corn products. However, silk and kernel expression in Northrup King's *Bt* corn will not likely increase the selection pressure for resistant ECB because it primarily feeds on the stalk, pollen, and leaf tissue.

In the southern USA, where corn and cotton acreage is in close proximity, there will be migration of the CEW from Northrup King's *Bt* corn to cotton (including *Bt* cotton). CEW only overwinters in roughly the southern half of the USA. CEW moths emerge from overwintering pupae and lay eggs on weeds. The next generation or two are in corn whorls and on corn silks and kernels. Moths emerging from this silk-stage generation migrate from corn to other crops including cotton. Evidence shows that CEW moths can migrate long distances, therefore each succeeding generation of moths may remain locally or individuals may be carried on wind currents to the northern states. In the South there are 3 to 6 CEW generations. In the North, there will usually be 1 or 2 generations. If there is silk expression of the CryIA(b) delta toxin at sufficient levels to select for resistant CEW, then resistant CEW could move from *Bt* corn to cotton/*Bt* cotton posing potentially significant problems in cotton or *Bt* cotton. Resistant CEW could lead to the failure of *Bt* foliar pesticides used on cotton or

to the failure of *Bt* cotton, *Bt* corn, and other crops both in the South and North.

The most critical part of the resistance management strategy is the high dose strategy coupled with an effective refugia. Evidence provided in the submitted resistance management plan for the high dose expression strategy in ECB is limited and is not necessarily representative of the selective conditions operating in the field. A high dose expression strategy will need to be validated in the field to determine whether the CryIA(b) delta-endotoxin will be produced uniformly at a high enough dose in the field to kill all susceptible individuals including heterozygotes. Without field validation, it is impossible to predict at this time the absolute success of the high dose expression strategy for ECB.

Possible high dose control exists for the first generation ECB on whorl stage corn, but not for later generation(s) on more mature corn plants. More data are needed on toxin expression in various parts of the plant at different stages of plant development. Silk and kernel expression in Northrup King's *Bt* corn will likely lead to a greater selection pressure being imposed on CEW than for existing *Bt* corn products. Lower expression as the plant matures and becomes senescent would not necessarily provide season-long high dose control for ECB. Evidence to date shows mixed results for suppression of CEW. Lack of a high dose would mean that ECB and CEW would be exposed to sublethal doses of the CryIA(b) delta-endotoxin. This would increase the likelihood for selection of resistance.

The Agency has rejected Northrup King's 5% non-*Bt* refugia in the north and 20% non-*Bt* refugia in the south option to prevent the development of ECB or CEW resistance because there are insufficient data. Industry, academia, and government experts have not come to an agreement on the appropriate size and structure for an optimal refugia. A "*Bt* corn consortium" met twice in 1995 (composed of USDA NC-205 (corn stalk borer entomologists), other academicians, and industry) and agreed that a minimum of 5 to 20% refugia was needed, but many opposed stating any figure until more is known. Silk and kernel expression in Northrup King's *Bt* corn will likely increase the selection for CEW resistance especially in cotton-growing areas. Silk and kernel expression in previously registered *Bt* corn products was insignificant and therefore of minimal concern. However, in the case of Northrup King *Bt* corn, these concerns are significant especially in parts of the country in which there is close proximity of corn and cotton acreage. In the cotton growing areas, the first generation CEW primarily feeds on weed hosts before funneling through corn in generations two +/- three. The CEW then fans out in later generations to attack cotton and other hosts for the rest of the season. Development on *Bt* corn with silk and kernel expression would subject a high percentage of the CEW, in additional generations, to resistance selection pressure. This will increase the likelihood of CEW resistance to *Bt* developing. There is also incidence reports of non-high dose *Bt* titer and survival of CEW on *Bt* cotton in 1996 to assess. Overall, in a benefits analysis it is likely that the losses to cotton from CEW resistance to *Bt* in the South and corn and other crops in the North, would greatly outweigh the benefits to field corn in the South. The reason for this is that should CEW resistance become established in the South, the northern areas of the USA will also have CEW resistance, because this species does not

17826

overwinter in the North, and the adult moths must migrate (blow in) from the South annually. Therefore, the Agency should take more preventative measures than for previously registered *Bt* corn products, i.e. limiting Northrup King *Bt* corn in cotton states and cotton-growing areas, until more data have been collected on refugia and CEW resistance risk.

VI. POTENTIAL BENEFITS

From information submitted by Northrup King, their *Bt* plant-pesticide produced in corn has been demonstrated to be effective against European corn borer (ECB). It is capable of replacing more toxic chemical pesticides registered to control ECB including: carbaryl, chlorpyrifos, carbofuran, fonofos, permethrin, esfenvalerate, methyl parathion, terbufos, and phorate. Additionally it should fit well into IPM programs.

The yield losses and acres treated for ECB appear to be documented. The percent yield increases gained from growing Northrup King's *Bt* plant-pesticide corn product compared with corn not producing the *Bt* delta endotoxin were not summarized in sufficient detail to evaluate the overall conclusions in the public interest finding statements submitted, but increased yields were demonstrated in several studies. While specific studies on growth and yield were not submitted (stand counts, etc.), the summary information submitted leads to the conclusion that no adverse effects on plant growth or yield are anticipated. This is sufficient information to conclude that increase yields will be derived from the use of the proposed product compared to non-treated corn, although quantification of this increase would require more detailed information.

Northrup King submitted a few studies involving other identified *Bt* plant-pesticide corn products. In the studies submitted that identified the other *Bt* corn products, specifically those registered to Ciba Seeds and Mycogen Plant Sciences, the Northrup King *Bt* plant-pesticide corn product was as good or superior to other registered products in control of ECB.

The human health effects assessment described in this document confirm the lack of toxicity of Northrup King *Bt* corn to humans. Therefore, toxicity to farm workers and applicators should be reduced as compared to those workers and applicators using conventional pesticides (and some conventional *Bt* sprays with a degree of acute toxicity) when used to control ECB in corn. While not mentioned in the Northrup King submission, there should be benefits from the lack of pesticide drift as compared to conventional sprays and granulars (but not other *Bt* corn products). The Northrup King *Bt* plant-pesticide corn products is no less toxic to humans than previously registered *Bt* corn products from other companies.

Economic benefits from Northrup King *Bt* corn will be dependent upon the price charged per unit (not provided) as compared to the price charged for average conventional corn varieties, other *Bt* corn products, the price of control of the target insects (including the price of application), and the relative yield increases per acre. This comparison has not been provided, and therefore, no conclusions can be made regarding these benefits.

VI. TERMS AND CONDITIONS OF THE AMENDED REGISTRATION

The following listing gives the terms and conditions of the amendment agreed to by Northrup King. The expiration date for the registration was amended to allow the registrant to complete the studies related to ecological effects and resistance management.

1. The registration will automatically expire on midnight April 1, 2001. EPA will reevaluate the effectiveness of Northrup King's resistance management plan before April 1, 2001 on whether to convert the registration to a non-expiring registration.

2. This registration is for field corn only.

3. Northrup King will:

a. unless demonstrated to EPA's satisfaction that alternative resistance management practices are equally or more effective than a structured refugia, develop and submit to EPA a draft plan for "structured" refugia by 8/9/98 and a final plan by 1/31/99;

b. discuss the development and implementation of the plan and alternative resistance management practices with EPA throughout development and implementation; and

c. implement the "structured" refugia plan or an EPA approved alternative resistance management plan no later than April 1, 2001.

4. Northrup King will monitor for the development of resistance using baseline susceptibility data and/or a discriminating concentration assay when such an assay is available. Northrup King will proceed with efforts to develop a discriminating concentration assay. Northrup King will ensure that monitoring studies are conducted annually to determine the susceptibility of ECB and CEW populations to the CryIA(b) protein. This resistance monitoring program will be developed to measure increased tolerance to *Bt* corn above the various regional baseline ranges. Annual reports of resistance monitoring will be submitted to the Agency by January 31 each year and include units sold per state of the Northrup King European corn borer protected corn. CEW, will be monitored for resistance in areas where ECB resistance is being investigated.

Populations of ECB and CEW will be collected from representative distribution areas of the registrant's *Bt* corn hybrids and monitored/screened for resistance, with particular focus on those areas of highest distribution in each State. The results of monitoring studies will be communicated to the Agency on an annual basis, by January 31 of the year following the population collections for a given growing season.

In addition, Northrup King will instruct its customers (growers and seed distributors) to contact Northrup King (e.g., via a toll-free customer service number) if incidents of unexpected levels of ECB & CEW damage occur. Northrup King will investigate and identify the cause for this damage by local field sampling of plant tissue from its hybrids and sampling of ECB & CEW populations, followed by appropriate *in vitro* and *in planta* assays. Upon Northrup King's confirmation by immunoassay that the plants contain CryIA(b) protein, bioassays will be conducted to determine whether the collected ECB or CEW population exhibits a resistant phenotype.

Until such time that a discriminating concentration assay is established and validated by Northrup King, Northrup King will utilize the following to define a confirmed instance of ECB & CEW resistance:

Progeny from the sampled ECB or CEW population will exhibit both of the following characteristics in bioassays initiated with neonates:

a. An LC50 in a standard CryIA(b) diet bioassay that exceeds the upper limit of the 95% confidence interval of the mean historical LC50 for susceptible ECB or CEW populations, as established by the ongoing baseline monitoring program. The source of CryIA(b) crystal protein standard for this bioassay will be *Bacillus thuringiensis* subsp. *kurstaki* strain HD1.

b. > 30% survival and > 25% leaf area damaged in a 5-day bioassay using CryIA(b)-positive leaf tissue under controlled laboratory conditions.

Based upon continued experience and research, this working definition of confirmed resistance may warrant further refinement. In the event that Northrup King finds it appropriate to alter the criteria specified in the working definition, Northrup King must obtain Agency approval in establishing a more suitable definition.

5. Northrup King will report all instances of confirmed ECB & CEW resistance, as defined above, to the Agency within 30 days. Upon identification of a confirmed instance of ECB or CEW resistance Northrup King will take the following immediate mitigation measures:

a. notify customers and extension agents in the affected area,

b. recommend to customers and extension agents in the affected area the use of alternative control measures to reduce or control the local ECB population, and

c. recommend to customers and extension agents in the affected area that crop residues be incorporated into the soil following harvest, to minimize the possibility of overwintering of ECB.

Within 90 days of a confirmed instance of ECB and/or CEW resistance, as defined above, Northrup King will: (1) notify the Agency of the immediate mitigation measures that were implemented, and (2) submit to the Agency a proposed long-term resistance management action plan for the affected area, (3) work closely with the Agency in assuring that an appropriate long-term resistance management action plan for the affected area is implemented, and (4) implement an action plan that is approved by EPA and that consists of some or all the following elements, as warranted:

a. Informing customers and extension agents in the affected area of ECB and/or CEW resistance,

b. Increasing monitoring in the affected area, and ensuring that local ECB or CEW populations are sampled on an annual basis,

c. Recommending alternative measures to reduce or control ECB or CEW populations in the affected area,

d. Implementing a structured refuge strategy in the affected area based on the latest research results. The implementation of such a strategy will be coordinated by the Agency with other registrants.

e. If the above elements are not effective in mitigating resistance, Northrup King will voluntarily cease sale of all of Northrup King's CryIA(b) corn in the county experiencing loss of product efficacy and the bordering counties until an effective local management plan approved by EPA has been implemented. During the voluntary suspension period, Northrup King may sell and distribute in these counties only by obtaining EPA approval to study resistance management in those counties. The implementation of such a strategy will be coordinated by the Agency with other registrants.

If EPA agrees that an effective resistance management plan has been implemented which mitigates resistance, Northrup King can resume sales in the affected county(ies).

6. Northrup King will maintain a (confidential) database to track its sales (units and location) of its *Bt* corn on a county-by-county basis, to the extent that such data are available. Northrup King will provide annually, on a CBI basis, sales data for each state indicating the number of units of *Bt* corn hybrids that it sells. This information will be provided by January 31 of the year following each growing season.

7. Northrup King will provide grower education. Northrup King has agreed to include an active partnership with such parties as: university extension entomologists and agronomists, consultants, and corn grower groups. Northrup King will implement a grower education program directed at increasing grower awareness of resistance management, in order

21826

to promote responsible product use. As specific resistance management recommendations are developed (e.g., as a result of ongoing research or experience) these will be incorporated, as appropriate, into the various grower communication and educational media. Northrup King will inform the Agency as it develops, implements, and refines its communication strategies. In addition to grower communication vehicles, Northrup King will also develop a Grower Guide, to be distributed to all customers, that will include current information regarding resistance management and integrated pest management.

8. Northrup King will confer with the EPA as Northrup King develops various aspects of its resistance management research program. Northrup King agrees, as a condition of this registration, to submit annually progress reports including results and conclusions from research (including scientific literature) as they become available in the following areas as a basis for developing a long-term resistance management strategy which include:

a. ECB pest biology and behavior including adult movement and mating patterns, larval movement, survival on silks, kernels, leaves, pollen, pith, and stalks, and overwintering survival and fecundity on non-corn hosts.

b. The feasibility of "structured" refuge options for ECB including both "block" refugia, "50-50 early/late season patchwork"; research needs to be done in both northern and southern areas on ECB.

c. Development of a discriminating concentration (diagnostic concentration) assay for field resistance (field screening) for ECB and CEW. Specific sampling locations will be established in each state to determine if increases in *Bt* toxin tolerance are occurring before crop failures develop. Increased tolerance levels need to be identified before field failure occurs. In monitoring for tunneling damage, the number of trivial tunnels may be less indicative of resistance development than the total extent of tunneling damage (e.g. length of tunnels). The extent of tunneling damage should be monitored as well as the number of tunnels.

d. Effects of corn producing the CryIA(b) delta endotoxin on pests other than ECB, including but not limited to CEW, fall armyworm, and the stalk borer complex.

e. The biology of ECB resistance including receptor-mediated resistance and its potential effect on population fitness, as well as the effects on insect susceptibility to other Cry proteins. Possible high dose control exists for the first generation ECB in the whorl stage, but not for later generation(s) on more mature corn plants. More data are needed on toxin expression in various parts of the plant at different stages of the plant in regard to ECB and CEW. This data will also be required of other secondary pests of corn (i.e. stalk borer

complex, fall armyworm, and southwestern corn borer) if EPA determines that research in section 8d above so warrants.

9. Label and Informational Material

Northrup King submitted a revised label incorporating the following revisions before registration:

a. Changing the name of the active ingredient to "*Bacillus thuringiensis* CryIA(b) delta endotoxin and the genetic material (plasmid vector pZ01502) necessary for its production in corn."

b. Adding the following requirements for 40CFR Section 156;
1. The signal word "Caution."
2. The "Keep Out of Reach of Children" statement.

c. Adding the statement: This plant-pesticide can not be sold or used in the states of Alabama, Arkansas, Florida, Georgia, Louisiana, North Carolina, Mississippi, South Carolina, and Texas. In addition, sale or use in the following counties within the indicated states is prohibited: Virginia (Greensville, Isle of Wright, Northampton, Southampton, Sussex, Suffolk Counties; Missouri (Butler, Dunkin); Mississippi (New Madrid, Pemiscot, Scott, Stoddard); Oklahoma (Bryan, Caddo, Canadian, Garvin, Grady); and Tennessee (Carroll, Chester, Crockett, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Henderson, Lake, Lauderdale, Lawrence, Lincoln, McNairy, Madison, Obion, Rutherford, Shelby, Tipton).

d. All corn that contains the plant-pesticide that is sold or distributed by Northrup King, or a cooperator of Northrup King, must be accompanied by Informational Material indicating the registration number, active ingredient, and the use restrictions mentioned above.

10. Northrup King may not sell or distribute any corn that contains the plant-pesticide in all counties of the following states unless specific prohibited counties are listed:

Alabama
Arkansas
Florida
Georgia
Louisiana
Mississippi
Missouri: Butler, Dunkin, Mississippi, New Madrid, Pemiscot, Scott, Stoddard Counties.
Oklahoma: Bryan, Caddo, Canadian, Garvin, Grady Counties.
North Carolina

South Carolina
Tennessee: Carroll, Chester, Crockett, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Henderson, Lake, Lauderdale, Lawrence, Lincoln, McNairy, Madison, Obion, Rutherford, Shelby, Tipton Counties.
Texas
Virginia: Greensville, Isle of Wright, Northampton, Southampton, Sussex, Suffolk Counties.

Northrup King will develop a resistance management program that is acceptable to EPA that includes the research specified in section 8a through e of this letter.

11. Collembola and *Daphnia magna* studies must be submitted by 5/14/97 for this active ingredient.

VII. RATIONALE FOR RECOMMENDATION

Pursuant to FIFRA section 3(c)(7)(B), EPA may conditionally amend the registration of a pesticide to permit an additional use if two criteria are fulfilled: 1) the applicant has submitted satisfactory data pertaining to the proposed new use; and 2) amending the registration in the manner proposed by the applicant will not significantly increase the risk of any unreasonable adverse effect. BPPD believes that both these criteria have been fulfilled.

A. Additional Use Amendment Under FIFRA 3(c)(7)(B)

The applicant has submitted or cited data to satisfy the first criterion for conditional registration under FIFRA 3(c)(7)(B). Northrup King has submitted or cited satisfactory data pertaining to the proposed additional use of the product in field corn, including the incremental risks that would result from approval of the applications. BPPD believes that the applicant has provided enough data to characterize the incremental risks associated with the development of resistance resulting from approval of their applications.

Although the data with respect to this particular new use is satisfactory, it is not sufficient to support an unconditional amendment under FIFRA 3(c)(5). Additional data is necessary to evaluate the risk posed by the development of resistance to Cry delta-endotoxins that is associated with generic use of these products. As discussed in more detail in section VI above, the introduction of these products for any wide-scale use poses the risk that pests, such as the ECB and CEW, will develop resistance to many different *Bt* microbial pesticides that are used on a wide variety of crops. BPPD believes that the applicants have submitted sufficient data to allow the Agency to determine that the applicants' plans to manage this risk will be workable for 2 to 4 years following initial commercial use of these products. Additional data, however, is necessary to determine how to effectively reduce the risks associated with resistance beyond that initial period. Consequently, BPPD recommends

imposing the data requirements specified earlier in this Decision Document in section VI.

BPPD also believes that the second criterion for a FIFRA 3(c)(7)(B) conditional registration has been fulfilled because it appears that the proposed addition use does not "significantly increase the risk of any unreasonable adverse effect." In essence, FIFRA requires a determination that the proposed additional use of these products for food and feed differs from the current use only in ways that would not modify the risk/benefit ratio so as to cause unreasonable adverse effects taking into account the economic, social, and environmental costs and benefits of the additional use as restricted by the terms and conditions of registration.

The proposed new use of this product for food and feed poses the risk of the development of multiple- and cross-resistance in certain Lepidoptera pests on corn. As a result pests could develop resistance to certain microbial *Bt* pesticides that are applied to both field corn and other crops and reduce the utility of such products. Microbial *Bt* pesticides are critical for many organic farming programs and are identified by the Agency as a safer pest control method than many chemical pesticide alternatives. The Agency further recognizes that microbial *Bt* pesticides have low dietary, worker, and ecological risks when compared to the more hazardous alternatives that might replace the microbial *Bt* pesticides should resistance develop. The microbial pesticides also are important components in many IPM programs for a variety of crops and the loss of such pesticides could cause growers to substitute more harmful pest control agents.

This amendment may provide substantial benefits to corn producers in the form of increased yields of field corn resulting from the control of damage caused by the ECB and possibly other corn pests.

The risks are substantial and BPPD has concluded that the risks, if unchecked, would outweigh the benefits of the proposed new use. However, the terms and conditions of the amendment that are recommended in Section VI of this Decision Document would mitigate the risks from pesticide resistance sufficiently so that the risks of the proposed amendment would not significantly increase the risks of unreasonable adverse effects. The registration will expire automatically in April 1, 2001. At that time EPA can re-evaluate whether the registrant has an effective resistance management plan. In the interim, the registrant must conduct a grower education program directed at increasing grower awareness of resistance management; conduct monitoring to help detect the development of resistance in ECB and CEW to the CryIA(b) delta-endotoxin and stop selling the product in areas where the registrant has detected resistance to its own product; conduct research to determine how to develop an effective long-term resistance management plan; and implement an EPA-approved structured refugia system. Growth in southern cotton regions is prohibited due to the risk of resistance developing to the CEW.

B. Existing FIFRA 3(c)(7)(C) Registration

The existing 3(c)(7)(C) registration is being amended as described above. Field corn seed increase and hybrid production use fall within the full commercial use and use restrictions under the original registration are superseded by the full commercial use amendment. However, the non-target data required under the original registration still are required.

VIII. RECOMMENDATION

The submitted data in support of this amended registration under section 3(c)(7)(B) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) have been reviewed and determined to be adequate. Studies and information regarding resistance management are included in the terms, conditions, and limitations of this registration. Amending the existing registration will not cause an increase in significant adverse effects to man or the environment, either as a result of exposure to non-target organisms or from the potential for the development of resistance.

Furthermore, the benefits of the new use pattern have been well established and the terms, conditions, and limitations imposed by this registration mitigate the risks posed from the potential pest resistance to *Bt*. Therefore, the potential benefits outweigh potential risks, i.e. from the development of resistance.

Based on the data submitted by Northrup King and reviewed by OPP staff, Biopesticides and Pollution Prevention Division recommends that Northrup King's plant-pesticide product containing the active ingredient *Bacillus thuringiensis* CryIA(b) delta-endotoxin and the genetic material necessary for its production in field corn be CONDITIONALLY REGISTERED for food and feed use under 3(c)(7)(B) of FIFRA.

CONCUR: _____

NONCONCUR: _____

DATE: AUG 5 1996