





Plant-Incorporated



US Environmental Protection Agency
Office of Pesticide Programs
Biopesticides & Pollution Prevention Division

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Protectants



US EPA Biopesticide Regulation

- U.S. EPA Office of Pesticide Programs
 - Registration Division & Science Divisions
 - Conventional chemical pesticides
 - Biopesticides & Pollution Prevention Division
 - multidisciplinary: Review Managers and Scientists
 - Biochemical Pesticides
 - Microbial Pesticides
 - Plant-Incorporated Protectants
 - www.epa.gov/pesticides/biopesticides



Biopesticides & Pollution Prevention Division

- Division Director: Janet Andersen
- Microbial Pesticide Branch Chief:
Dennis Szuhay
- Senior Scientists
 - Toxicology/human health: John Kough
 - Ecological effects: Zigfridas Vaituzis
- Specialist scientists
 - Gene flow: Tessa Milofsky
 - Insect Resistance Management: Sharlene Matten



Plant Incorporated Protectants



- Regulated by USDA, FDA, and EPA
- New 40 CFR part 174
- System based on Sound Science and Transparency
- Regulation of both the Gene and the Pesticide Produced
- All Proteins thus far



Pesticides

- US Pesticide = any substance intended for mitigating a pest or intended for use as a plant regulator, defoliant, or desiccant
- Plant Incorporated Protectants = a pesticidal substance that is intended to be produced and used in a living plant, and the genetic material to produce it.



PIPs Process

- Transparency
- All applications announced in FR
- All non-cbi data publicly available during the review process
- Numerous public meetings and Science Advisory Panels
- Extensive Use of Website



Risk Assessment

- Hazard
 - Toxicity
- Exposure
 - Scale of use, use patterns, application rates
 - Persistence, degradation, mobility
 - Population dynamics, infectivity, gene transfer
- Risk
 - Non-targets, humans, endangered species, domestic animals



Data Submission for Protein Plant-Pesticides

- **Product Characterization**
 - source of the gene and /expression system
 - nature of pesticidal substance
 - modifications to introduced trait
 - biology of recipient plant, stability of the introduced traits
 - test substance equivalence
- **Toxicology**
 - acute oral toxicity
 - mode of action
 - allergenicity screening
- **Exposure & Non-target Effects**



Testing of PIPs

- Product characterization
 - Source of the genes
 - What protein(s) are made
 - Expression- In what parts of the plant are the proteins found and at what level
 - Includes review of any marker genes



Testing PIPs (continued)

- Human health
 - Exact structure of the protein including amino acid sequence
 - Similarity of this protein to any known toxin or allergen
 - Toxicity testing—feeding the protein to mice
 - Stability/breakdown of protein in digestive fluids



Testing PIPs (continued)

- Ecological effects
 - Effects on non-target organisms
 - birds
 - fish
 - aquatics
 - invertebrates
 - Endangered Species
 - Monitoring



Testing PIPs (continued)

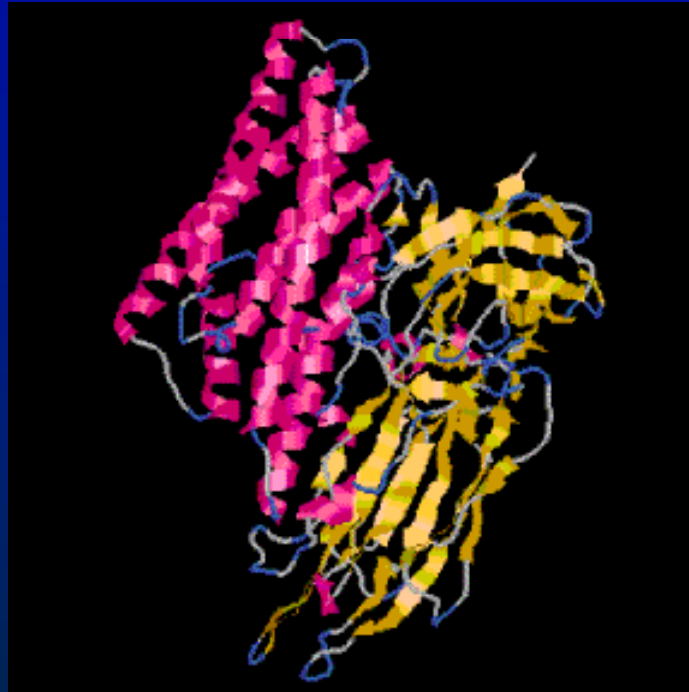
- Environmental fate
 - Protein expression
 - Protein persistence and degradation
 - Gene transfer



EPA Tox-Assessment Data

Mode of Action: Pore Forming Toxin

Cry1Ab



Swiss-3Dimage



EPA Eco-Assessment Data

- **Cry1Ab**

- Acute oral mice

- no effect >4000mg/kg
 - no effect >3280mg/kg
 - no effect >5050mg/kg

- Acute oral quail

- no effect >100,000ppm (Corn meal)
 - no effect >2000mg

- Catfish

- no effect at 100% of diet (Corn meal)



EPA Eco-Assessment Data

- Cry1Ab (continued)
 - Daphnia
 - no effect >150mg/l
 - Green lacewing larvae
 - no effect >20ppm
 - Parasitic wasp
 - no effect >20ppm
 - Ladybird beetle
 - no effect >20ppm
 - no effect (in pollen)



EPA Eco-Assessment Data

- Cry1Ab (continued)
 - Honey bee
 - Adult no effect > 20ppm
 - Larvae no effect > 20ppm
 - Larvae no effect (in pollen)
 - Collembola
 - no effect > 200ppm
 - LD₅₀ 240mg/kg/soil NOEL 125mg/kg/soil
 - Earthworm
 - nontoxic > 200ppm
 - nontoxic



EPA Eco-Assessment Data

- Cry1Ab Expression Data
 - Degradation – Bioactivity half life
 - Pure Cry1Ab plus soil 8.3 days
 - Cry1Ab expressed in corn - 25.6 days
 - Cry1Ab in corn plus soil 1.6 days



EPA Eco-Assessment Data

- Cry1Ab Expression Data
 - Expression levels – avg. protein ug/g fresh tissue from corn

	Lab	Field	Construct 1 - Highest levels in seedlings, declined thereafter through senescence. No detectable levels in silage.
Leaf	1.3	9.35	
Pollen	Not detectable	0.09	
Seed	0.57	-	Construct 2 – Highest levels in leaves at physiological maturity (25 days), declining thereafter.
Grain	-	0.31	
Whole plant	1.77	4.15	



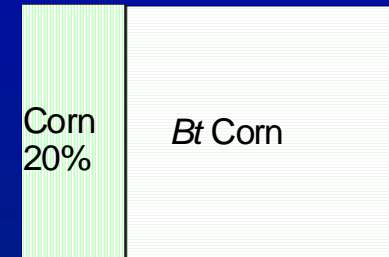
Testing PIPs (continued)

- Resistance Management
 - EPA requires an insect resistance management (IRM) plan for each Bt product
 - Required reports on compliance and adoption
 - Research and monitoring requirements

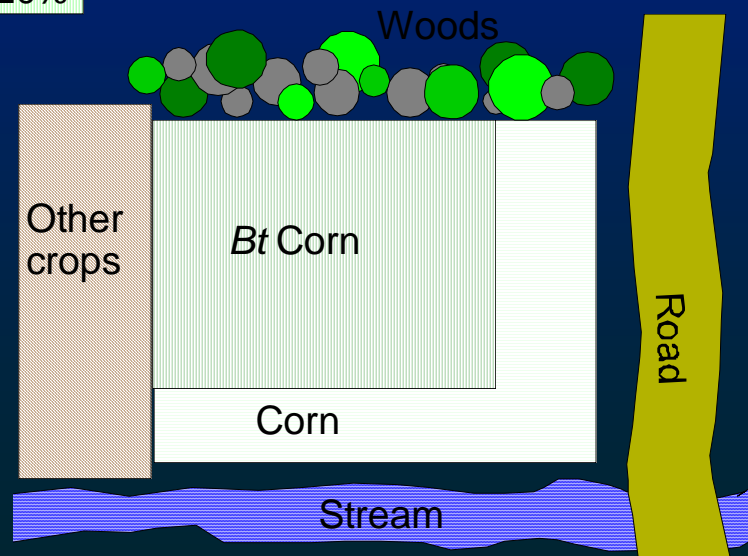


Refugia and Buffers

- Side by side refuge
- Separated refuge
- Refuge combined with barriers



1/4 mile





Cotton/B.t.

- Hazard assessment
 - Non-target species
 - Nontoxic to birds
 - Nontoxic to beneficial insects
 - wasps, lacewings, honeybees, ladybird beetles
- Exposure Assessment
 - no exposure to endangered species
 - estimated 1.44gm protein in soil/acre
 - undetectable in cottonseed meal
 - almost undetectable in pollen
 - not detectable in nectar
 - gene transfer to other plants (cotton)
 - wild/feral cotton: Arizona-sterile offspring
 - Hawaii, Everglades & Florida Keys
 - labeling: no commercial use





Registered Products

Bt Cry3A	Potato	Monsanto	1995
Bt Cry1Ac	Cotton	Monsanto	1995
Bt Cry1Ab	Corn	Syngenta	1996/8
Bt Cry1Ab	Corn	Monsanto	1996
PLRVreplicase/Cry3A	Potato	Monsanto	1998
Bt Cry1F	Corn	Dow/Mycogen	2001
Bt Cry1F	Corn	Pioneer/Dupont	2001
Bt Cry2Ab +Cry1Ac	Cotton	Monsanto	2002
Bt Cry3Bb1	Corn	Monsanto	2003
Bt Cry3Bb1+Cry1Ab	Corn	Monsanto	2003
Bt Cry1Ac + Cry1F	Cotton	Dow	2004
Bt moCry1F	Corn	Dow/Mycogen	2005
BtCry34Ab1+ Cry35Ab1	Corn	Monsanto	2005





Benefits example

- Corn Rootworm control is the highest insecticide usage in the U.S.
- Many corn rootworm pesticides are of concern to the Agency. Incidents, Restricted Use Pesticides
- New Bt Corn Rootworm products offers substantial environmental benefits (Cry3Bb1 & Cry 34/35)
- Syngenta also has a pending corn rootworm product and there are two pending multiple pest products from Dow & Pioneer.



Conclusions

- EPA has a strong regulatory review process
 - Transparency
 - Sound Science
- EPA's web site and other efforts keep the public informed about its decisions
<http://www.epa.gov/pesticides/>
- **The US Biotech Database lists products**
<http://usbiotechreg.nbii.gov/>