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

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Final Technical Consideration of Ciba-Geigy's Resistance Management Plan for Transgenic Corn Experimental Use Permit

FROM: Pesticide Resistance Management Workgroup[1] Janet L. Andersen

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The Pesticide Resistance Management Workgroup (PRMW) has reviewed Ciba-Geigy's resistance management plan for corn engineered to produce Bt toxins. The genetically engineered corn is designed to control lepidopterous pests, primarily European corn borer (*Ostrinia nubilalis* (Hübner)). We do not believe resistance to Bt would become a problem during the first year of the EUP because of the limited acreage involved.

We commend Ciba-Geigy for including in its EUP application a resistance management plan. This memorandum represents the PRMW's technical evaluation of the resistance management plan. At this time the Agency currently has no formal policy or test guidelines on pest resistance management.

1. General Overview of the Ciba-Geigy Plan

Without a more detailed description of Ciba-Geigy's plan it was not possible to complete a thorough assessment of the company's program. Based on the limited information provided and some contact with the registrant, we agree with the basic elements upon which Ciba-Geigy has developed its plan.

The Ciba-Geigy plan as presented in the EUP application is a strategy based on four tactics (Table 1). These tactics could be expected to be used in almost any resistance management plan developed for crops producing Bt toxins[2]. The Workgroup believes, in principle, the basis for the use of these tactics is correct. However:

- The four tactics by themselves may not be sufficient to prevent or delay Bt resistance;
- Based on preliminary data, it appears that the level of expression of the Bt gene described by Ciba-Geigy may not be sufficient to prevent development of Bt resistant pests; and

- ▸ Ciba-Geigy has included as part of its management plan, reliance on a multiple genic system; however, it has only submitted a single gene system in its EUP application to the Agency. Furthermore, based on limited information, it is unclear to what extent a system having multiple genes expressing Bt toxins will provide any additional restraints to the development of resistance.

A resistance management program, which could prevent or significantly delay the onset of resistance, would likely include tactics in addition to those suggested by Ciba-Geigy (Table 1). These additional tactics could be integrated into Ciba-Geigy's program without disrupting the existing strategy and should provide added protection. The last tactic listed in Table 1 can be technically and economically difficult to develop and may or may not be useful in Ciba-Geigy's resistance management program.

Table 1. Primary Elements of a Resistance Management Program for Transgenic Corn[3]

Tactic	Ciba-Geigy	Additional Tactics
High level of expression	✓	
Refugia	✓	
Integration of conventional and biotech resistance factors	✓	
Integration of multiple Bt genes	*	
Target agronomic practices		✓
Target IPM practices		✓
Resistance monitoring		✓
Tissue-specific or temporal expression	?	✓

* Although Ciba-Geigy has stated they consider this tactic a part of their resistance management plan, it is unknown when this will be available.

Explanation of resistance management tactics:

High level of expression: Nearly 100% of heterozygotic individuals containing the resistance gene are killed, thereby avoiding selection pressure for these individuals and the subsequent creation of populations of homozygous resistant pests.

Refugia: Host plants within or near the field that do not contain the plant pesticide and/or are not treated with the pesticide to control the target pest. These would allow homozygous sensitive pests to survive and contribute their genes to subsequent generations. For example, in the case of Bt corn, refugia may consist of corn plants in the field that do not contain the Bt gene.

Integration of conventional and biotech resistance factors: Secondary plant compounds or morphological changes that provide a level of host plant resistance are added to transgenic plants using traditional plant breeding techniques to those introduced by genetic engineering procedures. A pest is less likely to survive exposure to two different toxins, or to overcome different resistance mechanisms.

Integration of multiple Bt genes: The plant is engineered to contain two or more genes that each code for a different pesticidal protein. Since a pest is less likely to survive exposure to two different toxins (particularly if the mode of action of these toxins is different), development of resistant populations is less likely than if only one gene is present.

Target agronomic practices: Changes in agronomic practices that delay or prevent the development of pesticide resistance. Examples could include discing of corn stubble to kill a percentage of surviving overwintering pest population and mowing areas adjacent to corn fields, for example, to reduce cover for adult European corn borer (ECB) populations.

Target IPM (integrated pest management) practices: Use of IPM practices that result in the delay or prevention of pesticide resistance development. Examples include scouting fields to determine pest levels, treating with pesticides only when necessary to prevent crop losses, and crop rotation.

Resistance monitoring: Monitoring of populations in treated fields to determine the frequency of pesticide resistant individuals. Continued resistance monitoring allows for observation of trends in pest susceptibility to pesticides and provides information on whether or not currently followed resistance management practices are slowing or preventing the development of resistance.

Tissue-specific or temporal expression of Bt toxins: In tissue-specific expression, the pesticidal protein is produced only in a certain part of the plant, such as the leaves or the roots. In temporal expression, the pesticidal protein is produced only at specific times during the growing season. Both types of expression can limit the total amount of pest exposure to the pesticide.

2. Analysis of Components of Ciba-Geigy's Plan

Effectiveness of Level of Bt Expression. Ciba-Geigy expects the high level of expression of the Bt gene to effectively block the development of resistance in ECB. To achieve this, the level of expression must be sufficient to kill a critical number of the heterozygotic resistant ECB larvae to ensure control with these transgenic corn varieties[4,5]. Until a Bt-resistant strain of ECB develops in the field or laboratory, it will be impossible to determine whether the level of Bt toxin currently being expressed is sufficient to block development of resistance. A simple test of the adequacy of the level of expression is to determine the efficacy of the variety against susceptible ECB. If the level of expression is high enough to kill the critical number of heterozygotic resistant individuals, it would kill essentially all exposed susceptible individuals.

Efficacy data submitted by Ciba-Geigy in its application for the EUP indicate the range of survival across 26 varieties of transgenic corn was 0 to 45%[6]. Typical mean survival rates were 20 to 30%. Survival of this magnitude by susceptible ECB larvae clearly demonstrates current levels of expression will not be high enough to control heterozygotic resistant ECB. From these data, it appears the current level of expression will be insufficient to prevent or delay the onset of resistance. Indeed, development of resistance may be accelerated rather than suppressed[7].

Refugia. The presence of refugia is widely considered to be an important factor in the prevention of pesticide resistance[8,9]. In the case of plants that produce Bt toxins, because 100% of a pest population in a field will be exposed to the toxin, the need for refugia is critical[10]. For corn genetically engineered to produce Bt toxins, it is not known whether refugia must be created within the field, or if refugia located adjacent to the field can be effective in managing resistance. Ciba-Geigy is actively pursing this question and has included in their EUP an experiment to determine the biological feasibility of creating refugia within a field by mixing transformed and non-transformed seed. Whether either tactic or a mixture of the two is needed may only be decided after several seasons of field testing or until widespread, unrestricted planting is allowed.

Integration of Multiple Bt and Other Genes Coding for Resistance. In the Background Document on Resistance Management, Ciba-Geigy stated transgenic plants containing additional insecticidal genes will be available before resistance to a single gene develops. Multiple gene strategies might be a useful tactic to prevent or delay development of resistant pests, but this is dependent on the speed with which Ciba-Geigy can develop transgenic plants containing multiple insecticidal genes.

Based on conversations and information supplied by Drs. Fred Gould[4] and Rick Roush[3], we believe resistance can easily develop to transgenic plants having a single gene for Bt expression. The likelihood for development of resistance to transformed plants having a single gene is even greater if the level of expression is rather low as described in section 2. Resistance development to even a single gene for Bt expression might inhibit the effectiveness of a multiple gene strategy using Bt-toxins with the same mode of action. Additionally, resistance to single gene products could reduce user confidence in the utility of other types of transgenic plants.

Furthermore, a system containing multiple genes that express relatively similiar toxins may not provide a significant additional barrier to the development of resistance, if cross resistance to the genes occurs[4]. A system relying on genes expressing toxins with differing modes of action would be more likely to prevent or delay the onset of resistance.

3. Document Benefits Accruing from Resistance Management Program

Including experiments on resistance management tactics in trials conducted under the EUP could provide Ciba-Geigy the opportunity to document economic and environmental benefits associated with transgenic corn. The development of resistance could seriously jeopardize any of the benefits of using corn that produces Bt toxins (i.e., reduction in number of insecticide applications and total volume of pesticides applied to transgenic corn; reduction in worker exposure; and increased net return to growers). Furthermore, the development of resistance could potentially result in increased application of conventional pesticides. Therefore, an assessment of the benefits would underscore the need for a resistance management program. It may be useful for Ciba-Geigy to document how its plan will maintain these benefits by managing resistance.

The Agency would encourage Ciba-Geigy to pursue further development of a more detailed resistance management plan. In addition, the EPA would appreciate any information that Ciba-Geigy could provide to document the economic and environmental benefits derived from the use of corn engineered to produce Bt toxins and how the resistance management program will preserve these benefits.

References

1. The Pesticide Resistance Workgroup is comprised of Janet Andersen (Leader), Neil Anderson (BEAD), Mary Jane Angelo (OGC), Pat Bagley (RD), Laurel Celeste (OGC), Tobi Colvin-Synder (BEAD), Paul Lewis (BEAD), Sharlene Matten (OPPTS), Alan Schreiber (BEAD), Bernice Slutsky (EFED), Doug Sutherland (BEAD), Dennis Szuhay (BEAD) and Gail Tomimatsu (BEAD)

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