Essential Steps to Prevent Resistance:

Bt-*Transgenic Corn Varieties*

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Summary of Key Points

The Goal Must be to Prevent Resistance, Not Manage It

Bacillus thuringiensis (*Bt*) is a uniquely valuable resource of great importance to American, indeed global agriculture. The goal must be to prevent – not manage – resistance in populations of European corn borer and other insect pests. To the extent we lack the knowledge needed to achieve this goal, public agencies should accelerate research efforts.

Genes susceptible to *Bt* are "public goods." No law grants a person or corporation the right to erode the pool of genes susceptible to *Bt*, despite valid patents covering the techniques used to move *Bt* endotoxins into new plant varieties.

Any goal short of prevention and any evidence of slippage in resolve in achieving it by industry or the EPA-USDA will reinforce scientific and consumer opposition to all GMO crops here and abroad. It will also make it very difficult to gain approvals for soon-to-be introduced transgenic corn engineered to protect corn from rootworm damage.

The Basis for EPA Approval of IRM Plans

IRM monitoring should be sufficiently sensitive to identify the early stages of the emergence of resistance. Monitoring protocols are "sufficiently sensitive" if they will identify increases in the frequency of either fully or partially resistant alleles in time to

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implement remedial actions that will prevent the emergence of stable resistance in pest populations.

Until more is known, the Agency must be conservative in its judgements and the requirements it imposes. EPA should insist upon a few extra years for the monitoring plan to confirm the first stages of resistance and for the industry to put in place remedial actions sufficient to stop resistance before it becomes a stable part of some pest population.

Events That Do Not Express a High Dose for Second and Third Generation ECB Control Must Not be Approved for Further Use

There appears to be acceptance of the "high dose" expression standard suggested by Dr. Fred Gould -- a high dose is 25-times the LC_{99} for susceptible insect strains (Gould et al., 1994). Until a consensus emerges around another number, EPA should adopt this as its provisional standard.

Event 179 and DBT-418 do not express a high enough level of *Bt* late in the season to qualify as delivering a "high dose." Continued use of low-dose *Bt*-corn varieties could cut the time required for resistance to emerge from 10 years to 1 to 3. This would leave little time for remedial actions and essentially no margin for error. It's a bad gamble, one that the industry should not entertain nor the EPA allow.

At a minimum, EPA should postpone for at least three years any further consideration of applications to extend the use of low-dose events.

Affected companies are not likely to welcome such an EPA decision. But the success of the overall effort to preserve the pool of genes susceptible to *Bt* is like a chain, no stronger than its weakest link. Approving continued use of low-dose events is unnecessary and would border on reckless under the current circumstances.

Critical Need for More Sensitive Monitoring Methods

Recently published research strongly suggests we do not know enough to design and manage an IRM plan that will prevent resistance with a high level of confidence. EPA and USDA must assure that ongoing research and monitoring efforts give growers, researchers, and the industry as much time as possible to fine-tune IRM strategies. In this instance, time equals degrees of freedom.

Managing and Paying for Resistance Monitoring

Monitoring to date has been fully controlled and financed by the companies offering *Bt*-transgenic seed for sale. Industry monitoring should be augmented in the future by public sector funded and directed efforts.

Research teams should be challenged to identify "worst case" circumstances heightening the likelihood of resistance and should develop targeted sampling and testing methods to apply in such cases.

Each major corn growing state should carry out a multifaceted resistance monitoring effort combining field-level trouble-shooting with high-quality, sensitive laboratory assays capable of detecting the presence and frequency of resistant alleles at a frequency of 1 in 1,000 or less. At least one ECB sample should be screened for each 1,000 acres of *Bt* corn planted.

Such state-level programs will augment and assure independent confirmation of the results of industry-sponsored monitoring and provide growers, seed dealers, insurance companies, consultants, and regulatory agencies with an impartial source of information on *Bt* field performance and resistance.

The cost of a public sector research and monitoring effort of this magnitude might approach $5.0 million per year. Such an investment is modest relative to the annual and long run benefits if the efficacy of *Bt* can be preserved, and is further justified by the importance of a steep and rapid learning curve in the design and implementation of IRM plans for transgenic plant-expressed protectants.

Size and Placement of Refuges

Science cannot deliver clear-cut advice on the optimal size, placement, and management of refuges. In the light of uncertainty, the EPA should insist upon prudence coupled with an intensive effort to learn as quickly as possible how to minimize the cost and inconvenience of refuge requirements.

There should be a single clear refuge requirement in each region; the option to maintain a larger, sprayed refuge should be dropped. Growers should manage both the *Bt*-transgenic and non-transgenic portion of fields with sound Integrated Pest Management (IPM) practices. Economic thresholds will sometimes be exceeded in the refuge. Growers should then be given the option of spraying the refuge under a prescription use program with a non-*Bt* insecticide.

The Industry plan overstates the difficulty growers would have in planting 75 to 80 percent of each field to a *Bt*-variety and 20 to 25 percent to a conventional variety. For years growers had to comply with 15 percent to 25 percent set aside requirements on the same fields being planted today to *Bt*-varieties. Most growers are likely to locate their 20 to 25 percent refuge acres on about the same parts of a field as allocated in past years to set-asides.

***Bt* Crops Should be Managed Within an IPM System**

Bt-transgenic varieties contain the seeds of their own destruction, it is up to farmers to use them in a way that keeps these seeds from germinating.

Benefits to farmers and impacts on the environment and public health are often driven more by how new technologies are used than by their intrinsic properties. At this time, cautious and strategic use of transgenic varieties is not what industry marketing departments have in mind, nor are farmers sufficiently skeptical. Too many still want to believe in one-dimensional "silver bullet" solutions to multilevel, interactive management problems.

As farmers rely more expansively across time and space on a single pest management tool, the greater the odds that resistance and other control problems will emerge.

The EPA-USDA Position Paper courageously and correctly calls for "Immediate and coordinated remedial action for suspected and confirmed incidents of resistance is necessary." This provision will be another key test of EPA and USDA resolve. The agencies must err on the side of action in the effort to preserve the susceptible gene pool.

But very little happens immediately in the world of pesticide regulation. The only practical way for EPA to assure that remedial action plans will be "immediately implemented" is for the conditional registrations to state what the remedial action plans consist of and when, and on what basis and by whom they must be initiated. It will be particularly important for the registration requirements to specify clearly the data that will trigger the initiation of steps called for in the plans.

The EPA-USDA paper asks a key question -- "What level of resistance should be considered significant enough to 'trigger' remedial action?" My answer is:

> Any statistically significant reduction in susceptibility should trigger remedial action. The scope and aggressiveness of actions should be progressively increased until the level of susceptibility is restored to, or near its baseline level.

The Goal and Focus of *Bt*-Transgenic IRM Plans

Given the unique value and critical importance of Bacillus thuringiensis (*Bt*) to American, indeed global agriculture, the goal must be to prevent – not manage – resistance in populations of European corn borer and other insect pests.

The National Corn Growers Association (NCGA) and Industry deserve credit for seriously engaging the challenge of preserving the efficacy of *Bt* toxins. The Industry Insect Resistance Management (IRM) plan states that its goal is to "preserve pest susceptibility to *Bt* corn for more than 15 years." (Vlachos, D., et al., 1999; accessible at <http://www.ncga.com>). While a step in the right direction, the Environmental Protection Agency (EPA) and the U.S. Department of Agriculture (USDA) must set forth clearly and persuasively the many reasons why this goal does not go nearly far enough.

Compelling evidence shows that *Bt*-based biopesticides are uniquely valuable and safe pest management tools for vegetable, fruit and row-crop farmers. In 1996, the last year that USDA data is available on vegetable crop pesticide use, there were almost 1.4 million acre-treatments made with *Bt* foliar insecticides to vegetable crops -- more than any organophosphate insecticide (National Agricultural Statistics Service, 1997). Only permethrin and methomyl were applied more commonly.

Given the major advances in *Bt* formulation stability and efficacy, and major cost reductions since 1996, the soon-to-be-released 1998 vegetable pesticide use data will no doubt show increases in reliance on foliar *Bt* biopesticides.[1] Especially in the southeast and the critical Florida winter vegetable production region, foliar *Bts* are the backbone of worm control programs in several high-value crops (personal communication, Dr. Charles Mellinger, Glades Crop Care). A review of NASS/USDA pesticide use data over the past decade suggests that without *Bt*, the number of applications of OP, carbamate, and synthetic pyrethroid insecticides in tomato, pepper, melon and other crops would likely rise from one to two per crop cycle to six to eight or more. The implications of such a profound shift upward in reliance on high-risk chemicals are ominous given that the Food Quality Protection Act is likely to place much stricter limits on such uses over the next three to five years.

Bt can and should remain so for centuries. Genes susceptible to *Bt* are "public goods" that belong to everyone. No law grants, nor does any person or corporation have the right to knowingly erode the pool of genes susceptible to *Bt*, despite valid patents covering the techniques used to move *Bt* endotoxins into plants and gain their expression in novel cultivars. A patent on a new antibiotic does not give a drug company license to irresponsibly promote excessive use of the new product, risking the loss of efficacy of all antibiotics.

For these reasons, 15 years is not good enough for farmers, for consumers and the environment, nor for the companies that have invested heavily in bringing improved foliar *Bt* sprays and *Bt*-transgenic technologies onto the market.

The EPA must adopt the ***prevention*** of resistance as the goal of resistance management plans and the standard against which the efficacy of plans is judged and remedial actions taken.

Any goal short of prevention, and any evidence of slippage in resolve in achieving this goal, either by industry or the EPA or USDA, will surely serve as a rallying point for critics of agricultural biotechnology here and abroad. Evidence of resistance to *Bt* in a target pest, even if partial, or further evidence of adverse impacts on non-target organisms like Monarch butterfly or soil microorganisms, will reinforce scientific and consumer skepticism and galvanize market opposition to all GMO crops.

[1] An analysis of changes in reliance on foliar *Bt* insecticides in vegetable production will be posted on the "Ag BioTech InfoNet" website (http://www.biotech-info.net) on or about July 25, 1999.

Bt-corn transgenic varieties should be and are going to be held to higher standards for resistance prevention and minimization of adverse environmental impacts. Failure to fully meet these standards could undermine the commercial viability of today's transgenic corn varieties. Soon-to-be introduced transgenic corn engineered to overcome damage from corn rootworms would, as a result, face a torturously difficult path in gaining U.S. regulatory approval and an even tougher time gaining market acceptance abroad.

The Basis for EPA Approval of an IRM Plan

EPA regulatory reviews of plant expressed protectants like *Bt* are subject to the regulatory provisions and precedents of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The EPA cannot establish a pesticide residue tolerance nor grant a registration for a new food crop use of a pesticide until the applicant has documented a method to reliably detect residues at the level sought in the tolerance petition. There must also be toxicological data showing that there is a "reasonable certainty of no harm" from exposure to the pesticide at the levels proposed for tolerances. If no such method existed, the Agency would have no basis to enforce the tolerance or assure the public that the food supply is free of potentially hazardous residues.

Under current law, the Agency has little choice but to apply the same principles and common-sense logic in evaluating the efficacy of registrant-submitted *Bt*-corn IRM plans. Before extending the conditional registrations for any *Bt*-corn variety, the EPA should be able to conclude, based on credible data and expert opinion that **–**

> **The monitoring component in an IRM plan is sufficiently sensitive to identify the early stages of the emergence of resistance. A monitoring plan is "sufficiently sensitive" if it will identify increases in the frequency of either fully or partial resistant alleles in time to implement remedial actions that will prevent the emergence of stable resistance in pest populations.**

Hence, the projected time period between recognition of the first signs of resistance and the evolution of stable resistance is a critical evaluation criterion and important scientific question that must be settled as IRM remedial action plans are evaluated and implemented. Because *Bt*-transgenic technologies do have such great potential to diversify the tools accessible to farmers, pervasive uncertainty requires EPA to proceed cautiously, as it does when setting a tolerance on a pesticide in the face of toxicological data gaps or evidence suggestive of adverse impacts on developmental processes.

> **Until more is known about corn insect pest movement and population dynamics, expression of *Bt* toxins in plant tissues and throughout a cropping cycle, and the genetic basis and temporal dynamics of resistant gene flow within and across populations, the Agency must be conservative in its judgements and the requirements it imposes.**

In the instance of *Bt*-transgenic crops, the EPA should insist upon a few extra years for the monitoring plan to confirm the first stages of resistance and for the industry to put in place remedial actions sufficient to stop resistance before it becomes a stable part of some pest population.

The EPA and USDA must sort through complex tradeoffs between the scope and projected effectiveness of the monitoring and remedial action components of the industry IRM plans. In general, the lower the frequency of resistant alleles and the more sensitive the assay used to determine changes in resistant gene frequency, the longer the time period is likely to be between identification of slippage in susceptibility and the emergence of stable, essentially irreversible resistance (Onstad and Gould, 1998a and 1998b).

There is also a relationship between the extent and aggressiveness of remedial actions, whether it is possible to reverse slippage in susceptibility and whether there will be sufficient time to do so. Aggressive remedial actions, implemented quickly upon the first evidence of resistance, will have a much better chance of restoring full susceptibility in a population than partial measures implemented incrementally and only in limited geographic areas.

The EPA has to take these tradeoffs and factors into account in judging the overall likelihood that an IRM plan will succeed and prevent resistance. It should continue to seek guidance from public sector experts in the field, including the NC-205 Committee (for details on past contributions from the NC-205 committee, see http://www.biotech-info.net/NC_205.html).

Low-Dose Events That Do Not Express a High Dose for Second and Third Generation ECB Control Must Not be Approved for Further Use

There appears to be a consensus among scientists that two currently registered *Bt*-transgenic corn events -- Event 179 and DBT-418 -- do not express a high enough level of *Bt* late in the season to qualify as delivering a "high dose." The EPA-USDA position paper, the NC-205 committee, ILSI, the SAP, among others state that a high dose-refuge strategy must be the foundation for IRM plans. EPA's conditional registrations of all *Bt*-crops state that an effective IRM plan must be in place by crop year 2001 in order for the Agency to grant an extension of the conditional registrations, or to grant a full Section 3 registration.

The first challenge for EPA is to state in regulations the level or range of *Bt* endotoxin expression that meets the "high-dose" criterion. Dr. Fred Gould has suggested that such a dose is 25-times the LC_{99} for susceptible insect strains (Gould et al., 1994). This is one of the key components of *Bt*-crop IRM plans that still is not settled. Clearly more research and discussion is needed among experts in the field to reach closure on this vital performance parameter.

The temporal dynamics of *Bt*-toxin expression in leaves and other tissues is the second issue EPA must face in setting “high dose” event performance standards. It is clear that toxin levels decline in all *Bt*-transgenic cultivars as plants mature and enter senescence, but when can toxin levels begin to decline and how fast can they decline without undermining the efficacy of high dose-refugia strategy? Some experts believe that a high dose maintained three to four weeks post-anthesis is adequate. Such a consensus should be incorporated in *Bt*-crop performance standards.

Just what constitutes a “high dose” is one of the many areas of significant uncertainty which justifies a prudent approach in the next few years, coupled with a marked increase in reliance on monitoring of actual field populations and careful applied field research. Monitoring, in particular, must play a much bigger role since in the final analysis, changes in the susceptibility of field populations is the one indicator which is completely unambiguous and decisive in terms of the true risk of resistance and need for remedial actions and their efficacy.

It appears the high dose requirement is not met in the case of Event 179 and DBT-418 *Bt*-corn varieties. The implications are ominous given the findings of Onstad and Gould, who conclude in a 1998 Journal of Economic Entomology article that –

> “If a high toxin dose cannot be achieved and a small fraction of homozygous susceptible and heterozygous European corn borer neonates survive on transgenic maize, then resistance can develop in 10-33% of the time required under the assumption of a successful high dose that kills all heterozygous neonates.” (Onstad and Gould, 1998a).

Based on the Onstad-Gould findings then, continued use of low- or moderate-dose *Bt*-corn varieties could cut the time required for resistance to emerge from 10 years to 1. Even if it only cuts the time period from 10 years to 3 years, it still collapses the response time for remedial action plans such that there would be far fewer remedial action options and essentially no margin of error. It’s a bad gamble and one which the industry should simply not entertain nor the EPA allow.

Accordingly, EPA should make it clear to Event 176 and DBT-418 registrants and their licensees the Agency’s commitment to sticking by the terms of its initial conditional registration. The Agency must take this action so that the registrants of these varieties and the many seed companies working with them can make appropriate plans to reduce the acreage devoted to seed production utilizing these events in the year 2000 crop season. At a minimum, EPA should postpone for at least three years any further consideration of applications to extend the use of low-dose events. In the interim, limited experimental use permits should be considered if the companies desire to explore resistance management options and build a scientific case for approval after the three-year moratorium applicable to low-dose events.

Obviously the affected companies will not welcome, and indeed are likely to vigorously oppose EPA’s decision to not extend the registrations for these two events.

The credibility of the Agency will be at stake, as will public and grower confidence in EPA's ability to stand up to political pressure from the biotechnology industry.

A decision to approve the two low-dose events will substantially increase the "worst case" scenarios against which the unproven high-dose and refuge IRM plan will be tested. The efficacy of the overall effort to preserve the pool of genes susceptible to *Bt* bioinsecticides and transgenic varieties is like a chain, no stronger than its weakest link. Approving continued use of low-dose events is unnecessary and would border on reckless under the current circumstances.

Critical Need for More Sensitive Monitoring Methods

Recently published research on the genetics of ECB resistance to *Bt* endotoxins raises serious questions about the design and effectiveness of the high-dose plus refugia strategy (Huang et al., 1999; Andow et al., 1999; Andow and Alstad, 1998). Put simply, we do not know enough to design and manage an IRM plan that will prevent resistance with a high level of confidence.

More sensitive monitoring methods and resistance gene screening assays are clearly going to be necessary in order to prevent resistance if current trends continue in terms of the acreage planted to *Bt*-transgenic varieties. Experts agree that more sensitive methods are needed urgently to establish the initial frequency of resistant or partial resistant genes (Marcon et al., 1999; Andow et al., 1998; Andow and Alstad, 1998; Bolin et al., 1998; ILSI, 1998). In addition, more sensitive methods will have to be deployed annually and more systematically across the Cornbelt in order to identify slippage in susceptibility early enough to reliably prevent resistance.

The discriminating dose method relied on in current registrant IRM plans is sensitive enough to identify a resistant gene present at a frequency of about 1 in 100. This translates into as high as a 1 in 10 frequency for the resistant allele within a population of European corn borers, and control failures are likely to then be just a few generations away.

A monitoring method that can reliably detect resistance only when present with a frequency of 1 in 100 leaves essentially no room for remedial action. Upon evidence of resistance using the discriminating dose method, a complete and immediate cessation of *Bt* selection pressure would be justified in order to restore susceptibility. Continued planting of any *Bt*-transgenic crop would be out of the question. Even more worrisome, applications of foliar *Bt* sprays might also have to be suspended in some areas where resistant insects are known to move from corn and cotton fields into vegetable or fruit crops. The legal basis and mechanics for suspending foliar *Bt* insecticide use on farms not planting any transgenic crops have not been explored and are, at best, dicey.

The lack of any time to implement more aggressive resistance management strategies would turn the *Bt*-corn industry into a high-stakes, year-to-year gamble. The costs associated with the emergence of resistance – which experts agree will be just a matter of time – will be high. If effective remedial actions are not taken and the efficacy of *Bt* is lost, the costs will be dramatically greater and very long-lived. Clearly, these costs would dwarf any benefits stemming from a few years, or even a few decades of the planting of *Bt*-transgenics.

For this reason, the EPA and USDA must assure that ongoing research and monitoring efforts in both the public and private sectors advance the state-of-the-monitoring art. Growers, researchers, and the industry need as much time to adapt and respond as possible; in this instance, time equals degrees of freedom. Specifically, EPA and USDA, in cooperation with the industry, should –

- Provide stable funding for a significant monitoring methods development research effort across several land grant universities and USDA research laboratories. This effort should be independent of private sector efforts also dedicated to improving monitoring methods and sensitivity.

- To hedge bets in ongoing monitoring efforts, the use of multiple screens and techniques, drawing upon the experience and ideas of scientists at several universities, should be supported financially until a consensus emerges on the best method or methods to use and the promulgation of affordable standard operating procedures.

- As a matter of some urgency to establish baseline levels of resistant alleles, much greater use should be made this fall and in the next crop year of the F_2 screen because of its ability to detect resistant genes at a frequency of 1 in 1,000 or less. Much heavier use should also be made of this screen in routine monitoring because of the added time it could provide to trigger action in refining and implementing IRM plans.

Managing and Paying for Resistance Monitoring

Monitoring to date has been fully controlled and financed by the companies offering *Bt*-transgenic seed for sale. Industry monitoring should be augmented in the future by two public sector funded and directed efforts.

As stated above, one should focus on developing new and more sensitive monitoring methods. Research teams should be challenged to identify “worst case” circumstances heightening the likelihood of resistance and should develop targeted sampling and testing methods to apply in such cases. The monitoring systems emerging from this work should strive to detect resistance genes at a frequency of 1 in 1,000 or less, and should be the standard against which other, lower-cost monitoring methods are judged.

The USDA and/or EPA should support a variety of approaches and research teams through a focused competitive grants program. The new biointensive IPM centers the USDA is planning on starting this fall could play a constructive role in getting this research off the ground quickly and fostering consensus within regions regarding the most desirable research strategies to pursue.

Second, each major corn growing state should carry out a multifaceted resistance monitoring effort focusing on the major corn growing areas and production systems in the state. These publicly supported programs would combine field-level trouble-shooting with high-quality, sensitive laboratory assays capable of detecting the presence and frequency of resistant alleles. Such state-level programs would –

- Augment and assure independent confirmation of the results of industry-sponsored monitoring on all aspects of the performance of *Bt*-transgenic varieties; and

- Provide growers, seed dealers, insurance companies, consultants, and regulatory agencies with an impartial source of information on the level of expression of *Bt* in transgenic cornfields, discriminating doses and levels of resistance, and plausible explanations for control problems or unexpected yield drag.

Public funding for a markedly expanded resistance research and monitoring effort is justified for the foreseeable future because of the importance of preserving the efficacy of *Bt* and the relevance of such work beyond management of *Bt*-transgenics. Lessons learned will help guide the design of resistance management plans for other plant expressed protectants, and will generate valuable information on the biology and management of a major corn insect pests that will no doubt be around for a long time.

The new program should support at least one multidisciplinary research project in each major corn growing state. At least for the next few years, the program should support an intensive monitoring effort. There should be some samples tested annually in each township with 20 percent of more acres planted to *Bt* corn, on the order of one assay per 10,000 acres of *Bt*-corn planted. The assays used should be sensitive enough to detect resistance genes present at a frequency of 1 in 1,000 or less. Until an improved screen is developed, the F_2 screen developed at the University of Minnesota, or equally sensitive variations of it, should be relied upon most heavily.

Total seed corn sales typically fall between $4 billion to $5 billion. If *Bt*-transgenic varieties account for as much as 30 percent of the market, sales will exceed $1 billion and could approach $2 billion. How much should be spent to protect the long-run viability of this technology? A $10 million monitoring program for the next few years would reflect just 1 percent of gross sales annually – not a huge investment. A program of this size would allow thorough annual monitoring of a half-dozen to a dozen locations around a state. Coupled with industry monitoring, there would be enough sampling undertaken to establish a reliable baseline within just a few years and to hopefully detect any significant slippage in susceptibility within a year of its occurrence. If there is no evidence of resistance after three or four years of sampling, the scale of the effort can be reduced by focusing ongoing effort on known, high-risk circumstances. By then the science-base should be sufficient to determine with greater precision what those circumstances are.

The cost of a significant public sector research and monitoring effort is modest relative to long-run benefits if the efficacy of *Bt* can be preserved, and is further justified by the importance of a steep and rapid learning curve in the design and implementation if IRM plans for transgenic plant-expressed protectants.

If federal funds are not forthcoming, growers and the industry should agree upon a check-off on each bag of *Bt* corn sufficient to support the same program. Just a small fraction of the technology fee would suffice. The funds should be allocated to the USDA and/or the regional pest management centers administering the competitive grants program and contracting for monitoring services.

Size and Placement of Refuges

Experts agree that refuges will help delay the emergence of resistance. In all likelihood, refuges will also play a critical role in multitactic IRM plans that are designed to prevent resistance.

Science cannot deliver clear-cut advice on the optimal size, placement, and management of refuges. A strong consensus exists that refuge requirements should be allowed to vary in different regions as a function of the presence of other Lepidopteran pests, the planting of other *Bt*-transgenic crops, and the importance of foliar *Bt*-bioinsecticide applications.

In the light of uncertainty, the EPA should insist upon prudence coupled with an intensive effort to learn as quickly as possible how to minimize the cost and inconvenience of refuge requirements. Requirements set forth in regulations should anticipate and allow with minimum transactions costs a degree of large-scale experimentation with refuge management through university-grower-consultant cooperative research programs.

The recommendations for refuge size set forth in the May 27, 1999 EPA-USDA Position Paper seem reasonable, as does the stated need to adjust refuge requirements in different regions (this position paper is accessible at <http://www.epa.gov/pesticides/biopesticides/otherdocs/bt_position_paper_618.htm>). But to simplify grower compliance, assist in compiling data on field performance and pest dynamics, and improve the likely effectiveness of refuges, EPA should make two key changes in refuge placement and management requirements.

EPA should drop the option of planting a larger sprayed refuge for the reasons set forth clearly in the Industry plan. There should be a single clear refuge requirement in each region. Growers should manage both the *Bt*-transgenic and non-transgenic portion of fields with sound Integrated Pest Management (IPM) practices. In some cases, despite use of recommended preventive IPM practices, insect economic thresholds will be exceeded in the refuge. When this occurs, growers should be given the option of spraying the refuge under a prescription use program with a non-*Bt* insecticide.

The prescription use program should be designed and carried out by a team of university specialists, augmented in certain tasks and drawing on the field expertise of crop consultants, growers, and industry experts as deemed necessary. It should be implemented on a pilot program basis for three years, at which point the need for and efficacy of the program would be evaluated.

Individual prescriptions should be granted or approved either by a university specialist or by an independent crop consultant trained and certified to carry out this function by the university team. The person providing the prescription should be responsible for scouting the field and recording key data on the variety planted, crop status and health, pest levels and damage, and any other information a state university team requires to help assess possible impacts on the evolution of resistance. These records will look much like a thorough scouting report done by a crop consultant. The report should be provided to the grower and the state specialist designated to oversee the prescription use program. Reports and/or summaries of their contents should be accessible to the company selling the corn variety, as well as researchers and interested members of the public, in ways that respect the rights and privacy of growers.

In addition to obtaining a prescription to spray a refuge, growers utilizing this option should in the next two crop cycles consult with crop consultants and university specialists regarding the size and placement of refuges, and the pattern of *Bt*-varieties planted on various fields. Adherence to recommendations provided in this consultative process would be a necessary condition for approval of any subsequent prescriptions allowing insecticide applications on refuge acreage in a subsequent crop season.

A second set of changes are warranted in the placement of refuges relative to parts of fields planted to *Bt*-transgenic varieties. The Industry plan overstates the difficulty growers would have in planting 75 to 80 percent of each field to a *Bt*-variety and 20 to 25 percent to a conventional variety. A near-optimal placement of the refuge would be the headlands on both ends of a field along with as many rows as necessary along one side of the field. Following such a planting pattern would be relatively simple. For years growers had to comply with 15 percent to 25 percent set aside requirements on the same fields being planted today to *Bt*-varieties. In all likelihood growers would locate their 20 to 25 percent refuge acres on about the same parts of a field as allocated in past years to set-asides. The ease and convenience to the farmer of meeting refuge requirements in this way makes this an attractive option to encourage grower compliance.

Whenever fields above a particular size are planted, say 100 acres, the EPA should impose stricter requirements governing the placement of refuges relative to *Bt*-transgenic acreage. At a minimum, refuge acres should be part of the field and placed at least on three sides, or in three distinct parts of the field. Alternative configurations should be allowed as long as the distance between any part of the *Bt*-portion of the field and the nearest portion of the refuge is kept below some maximum threshold. University experts should be called upon to set this distance and provide detailed guidance in the placement of refuges in the case of large fields.

Managing *Bt* Crops Within an IPM System

The EPA-USDA Position Paper sets forth nine “Best Management Practices” that should “…be used as guidance in developing IRM strategies for *Bt* crops.” Two call for farmers to employ prevention-based Integrated Pest Management Systems (IPM) when growing *Bt*-transgenic varieties.

I commend the agencies for recognizing the importance of the overall IPM system used to manage corn insects. In the final analysis, the performance and sustainability of *Bt*-transgenic crops are going to be determined by how farmers deploy these technologies within multitactic IPM systems. *Bt*-transgenic varieties contain the seeds of their own destruction, it is up to farmers to use them in a way that keeps these seeds from germinating.

With most applications of agricultural biotechnology, benefits to farmers and impacts on the environment and public health are driven by how the technologies are used more so than their intrinsic properties. Put differently, one can imagine circumstances and ways in which most imaginable agricultural biotechnologies can be utilized on the farm with positive and sustained benefits for farmers, the environment and the public. Regrettably though at this time, such strategic use of transgenic varieties is not what industry marketing departments have in mind. Some farmers are also at fault for not heeding the lessons of the past. Many are still quick to believe in “silver bullets” despite the lessons of the past, and allow short-term goals and pressures to drive decisions that should instead be more responsive to longer-term needs and consequences.

In general, as farmers rely more expansively across time and space on a single pest management tool, the greater the odds that resistance and other control problems will emerge, and the more likely the prospects that the technology will lead to environmental outcomes serious enough to trigger additional regulatory scrutiny.

Increasingly wild swings in the marketplace and the lack of discipline in the adoption of new technologies places EPA in a quandary. Should it assess IRM plans and otherwise regulate based on the “worst case” circumstances that would arise if farmers rely excessively on a given control technology? Should the agency presume that farmers will utilize biotechnologies in the context of multitactic IPM systems, as recommended, thereby avoiding “worst case” adverse outcomes that might warrant regulatory restrictions?

The EPA-USDA Position Paper anticipates these problems and at least calls for *Bt* IRM plans to be consistent with IPM. But the EPA needs a much better reason and firmer basis to ignore high-risk scenarios. An undefined, non-binding recommendation will not suffice. Prescription use is one option. Other novel options need to be explored whereby product approvals, labels and technology agreements specify the essential features of the agronomic and pest management systems in which a given biotechnology may be used. Absent a mechanism to do so and willingness to confront these issues, EPA will have no choice but to regulate based on plausible "worst case" circumstances. These will, of course, include rapid and widespread adoption in the absence of a proven IRM plan, i.e., the status quo.

There are other, pragmatic challenges ahead if the IPM-related BMPs for *Bt*-transgenic IRM plans are to be meaningful. The reason for requiring growers to use IPM is to prevent pest populations from building to a level sufficient to trigger the need for a treatment intervention, and to spread the control burden widely across a number of different tactics and inputs. Diversifying control tactics is one of the key elements of any resistance management plan.

EPA and USDA need to provide a more thorough and convincing discussion of the relationship between the planting of *Bt*-transgenic corn and IPM, especially since these agencies are explicitly recommending that *Bt*-corn be managed within an IPM system. The core principle of IPM is that no treatment interventions are made until field scouting shows that a pest population has reached a threshold level where the cost of control is less than the expected loss of income from pest damage.

USDA needs to specify with greater clarity what specific practices, under what circumstances are considered necessary in managing ECB and *Bt*-transgenics within the context of IPM. In addition, USDA needs to anticipate and discuss the potential conflicts between recommended IPM practices and the BMPs that university specialist might recommend as part of a remedial action plan when evidence of resistance has surfaced in an area. One logical response would be to eliminate selection pressure. This would require a halt of further plantings of *Bt*-transgenic crops and applications of foliar *Bt* products, coupled with aggressive efforts to reduce ECB populations through crop rotations, the management of crop residues, and applications of conventional pesticides. BMPs in the context of a remedial effort to restore susceptibility will clearly differ from routine IPM practices. USDA and EPA should provide guidance and support in advance to the university teams who will have to work through the differences with growers, most likely on short notice and under significant and conflicting pressures from various stakeholders.

The sixth "Best Management Practice" that the EPA-USDA Position Paper calls for in IRM plans states that "Immediate and coordinated remedial action for suspected and confirmed incidents of resistance is necessary." EPA and USDA are correct, and indeed courageous to call for immediate action even in cases of suspected resistance. This provision will be opposed by many in industry as "over-reacting" and sets the stage for another key test of EPA and USDA resolve. The agencies must hold the line and err on the side of action to preserve the susceptible gene pool, at least for the next few years.

But how will EPA and USDA accomplish this goal? Very little happens immediately in the world of pesticide regulation. The only practical way for EPA to assure that remedial action plans will be "immediately implemented" is for the conditional registrations to state what the remedial action plans consist of and when, and on what basis and by whom they must be initiated. It is not necessary for the EPA-USDA to specify all the details needed in the plans in various regions. The proposal to have regional centers or groups like NC-205 further develop and help implement the plans following guidelines set out by EPA and USDA is a sound one. EPA and USDA should, however, retain the authority to review and modify the plans applicable to different areas or circumstances.

The registration requirements should also specify clearly the data that will trigger the initiation of steps called for in the plans. Someone will ultimately be responsible for making the judgement that a given set of information rises to the level of evidence necessary to invoke the plans. The EPA and USDA must carefully consider who will be given this responsible. If it is an organization or committee other than EPA, the agencies must assure that the responsible party is given adequate insulation from the criticism and professional repercussions that can sometimes follow the imposition of unpopular restrictions on agricultural inputs.

Specific Questions Posed for the Monitoring and Remedial Actions Panel

The EPA and USDA have posed a series of questions to panelists. In addition to suggestions offered above, I offer the following answers to some of the specific questions raised.

Question: "What should be the goals for a national/regional monitoring program?"

Answer: The basic goal must be to prevent resistance from ever getting established in a target pest population. To achieve this goal, monitoring activities must serve two purposes –

- First, the establishment of accurate baseline frequencies of fully and partially resistant alleles in target pest populations; and second
- Identification of slippage in susceptibility in time to allow for remedial actions to restore the susceptible gene pool to, or close to its original state.

The more sensitive the monitoring program, the more time growers and the industry should have to refine and implement IRM plans sufficient to prevent resistance from becoming stable in any target pest population. The more aggressive and effective the remedial action plan, the shorter the period needed between identification of resistance and the initiation of remedial actions.

Question: "Who should coordinate a national monitoring program?"

Answer: EPA and USDA should jointly specify the performance parameters the monitoring program should meet and how samples, assay results, and other information should be collected, reported to EPA and USDA, made available to researchers and the industry, and shared with the public.

State agricultural experiment stations should be responsible for carrying out field collection and laboratory assay work, and for sharing results widely. A good option would be use of an Internet website patterned after the Cooperative Extension sites that several universities now use to report the results of assays on resistance to pesticides. A jointly established EPA-USDA committee of stakeholders should coordinate the program. Key program performance parameters, functions, guidelines and principles should be embodied in the provisions of cooperative funding agreements between the USDA and agricultural experiment stations.

Question: "What is the minimum planting density (market penetration) of any *Bt* crop that should be monitored?"

Answer: Resistance can emerge from a single farm or field and spread from there despite the best efforts of other growers to combat it. The key issue is not market concentration, it is the management of *Bt*-transgenic acreage planted in fields large enough to lead to resistance. For all intents and purposes, all commercial acreage should be monitored.

Question: "How should samples be collected…assays performed…"

Answer: USDA and EPA should establish an Advisory Committee by this fall to offer by next year detailed guidance in the structure of a sampling and monitoring program sufficient to achieve the program's overall monitoring goals. In crop year 2000, sampling and assay work should be carried out in compliance with these draft protocols. By crop year 2001 if EPA decides to extend the registration of any *Bt*-transgenic varieties, the Agency should promulgate detailed standard operating procedures and GLPs governing all facets of resistance monitoring.

Question: "What level of resistance should be considered significant enough to 'trigger' remedial action?"

Answer: Any statistically significant reduction in susceptibility should trigger the initiation of remedial actions. The scope and aggressiveness of the actions should be progressively increased until the level of susceptibility is restored to, or near to its baseline level. This may require a temporary (two to five year) regional ban on further plantings of *Bt*-transgenics.

The criteria for termination of remedial actions should be a return to some high percent of baseline susceptibility; on a provisional basis until better information is available, a return to 90 percent susceptibility would be prudent and probably achievable. This would correspond to no more than a 10 percent increase in the frequency of the resistant allele in surveyed populations, assuming access to credible baseline data on the frequency of the naturally resistant allele.

Alternatively, if future research establishes a threshold for the frequency of resistant alleles below which IRM plans are very likely to prevent any slippage in susceptibility, remedial action can be ended when this threshold is achieved, even in the absence of baseline data on the frequency of the resistant allele.

Question: "How should multiple *Bt* crops with shared pests be handled in terms of resistance monitoring?"

Answer: Conservatively and very carefully, with heightened effort to establish baseline resistant allele frequencies and more intensive monitoring to check for increases in whole or partial resistance genes. The basic goal and the standards applied should be the same; the level of effort should be enhanced, particularly in areas where vegetables are grown, or where vegetable pests are known to spend part of their life cycle.

Question: "Discuss the pests that should be monitored for resistance."

Answer: In addition to the target and non-target pests properly noted in the EPA-USDA Position Paper, recent evidence heightens the importance of monitoring resistance in soybean loopers. A team of Louisiana researchers has shown that soybean loopers can move between soybean, cotton and corn fields, and that selection pressure associated with *Bt*-transgenic crop varieties has contributed to higher discriminating doses for foliar *Bt* products (Mascarenhas, R.N. et al., 1998). They express strong concerns that *Bt*-transgenic plantings will trigger resistance in a number of insects that are either already or may become soybean pests.

Question: "What should be done in cases of confirmed resistance?"

Answer: The remedial action plan steps already set forth and agreed upon should be invoked including, at a minimum, immediate cessation of any further planting of *Bt* varieties, steps to isolate the resistant population, and biointensive IPM management practices designed to reduce populations as significantly as possible. In special cases, the EPA and USDA may also need to work with growers in the affected area to bring about a voluntary or mandatory suspension of applications of foliar *Bt* pesticides.

In such circumstances, affected growers should be compensated by the industry for crop losses, increased pest management costs, or other loss of income directly caused by the unavailability of *Bt* insecticides. The EPA and USDA should seek guidance from the industry in establishing the most cost-effective and equitable mechanism to establish a fund to cover such claims.

Question: "Discuss annual surveys to measure grower compliance."

Answer: Other than the addition of appropriate questions in routine NASS/USDA chemical and cropping practices surveys, no additional effort is warranted by government agencies to enforce or assess grower compliance with IRM plans. The linkage between compliance and the effectiveness of IRM plans is far too tenuous at this time to justify any additional public expense. Instead, available public resources should be invested in much more intensive research and monitoring efforts as described. The true impact and adequacy of IRM plans can only be judged by carefully monitoring the frequencies of resistant alleles in the field.

Thank you for the opportunity to offer these comments.

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