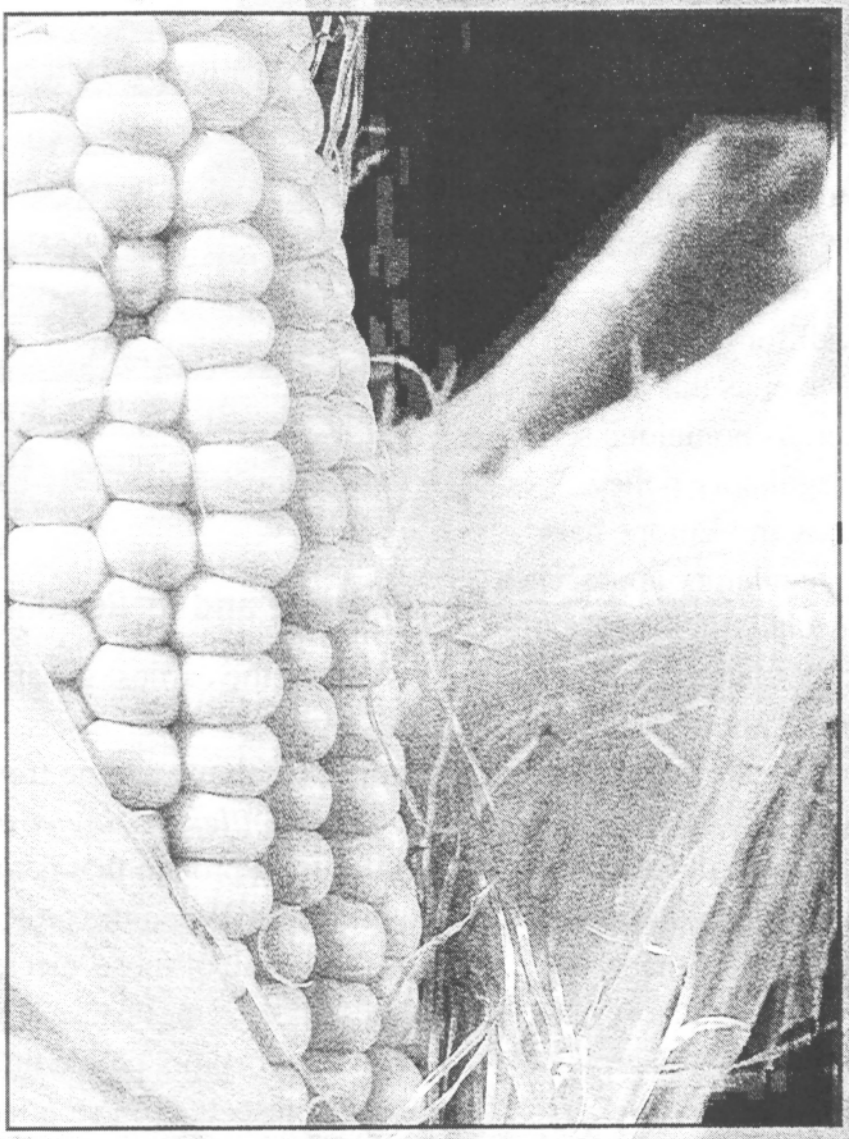
Regulating Bt Maize in the United States and Europe



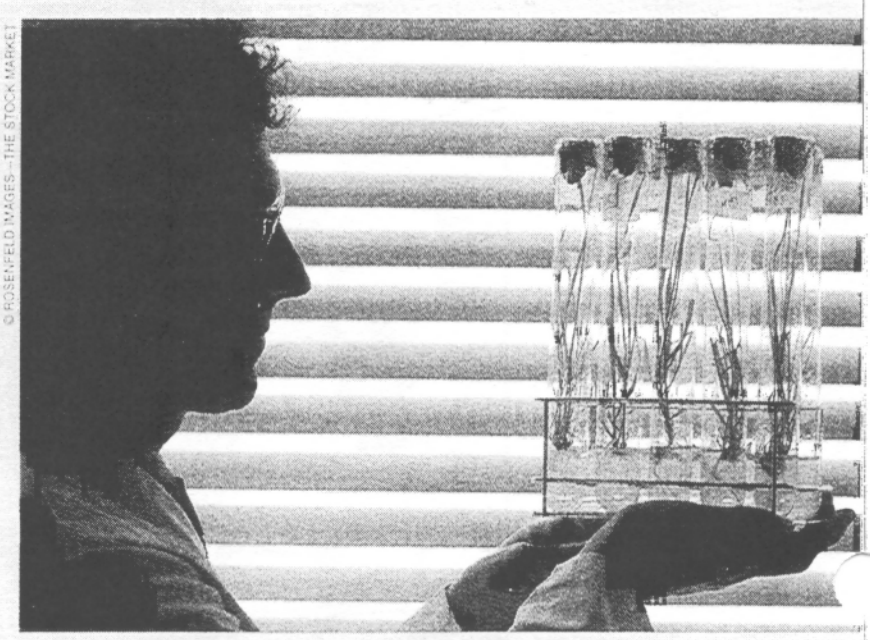
A Scientific-Cultural Comparison

by Les Levidow

The commercial cultivation of genetically modified (GM) crops has become big business. Such crops offer the potential benefits of higher yields and lower agrochemical usage, but they may also harm agriculture, the environment, and human health. Governments around the world are attempting to fashion regulatory policies to maximize the benefits and minimize the risks of these crops. Proponents of genetically modified crops call for "science-based regulation," yet as this article demonstrates, there is no unique scientific basis for regulatory policy.

The United States and Europe have devised different regulatory approaches to GM crops, especially in the case of maize (corn) that has been genetically altered to protect it from insects. In brief, U.S. regulation has emphasized the risk of insect resistance, for which extra controls have been developed. By contrast, the European Union (EU) has taken no responsibility for that risk, though some national regulators have cited a wide range of risks as grounds for imposing extra controls.

This article compares the regulation of Bt maize in the United States and Europe to illuminate the reasons for the different responses. Such understanding can inform policy debates and perhaps suggest ways toward better procedures.



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Bt Maize and Its Regulatory Context

Among the earliest genetically modified products were "insect-protected" crops containing a gene from the bacterium *Bacillus thuringiensis* (Bt) that codes for a protein that is toxic to certain insects. When the protein is ingested by the larvae of those species, their digestive enzymes cause it to bind to specific receptors on the intestinal lining; the insects soon stop feeding and may die. Biotechnologists first inserted this gene into the microorganism

Pseudomonas, which was then sprayed on the leaves of crops as an alternative to artificial insecticides. Later they inserted the gene directly into the genome of important crops such as cotton, potatoes, and maize. This was a significant advance because the protection conferred by spraying tends to be short-lived whereas a genetically modified plant produces the toxin continuously. (For more on the process of genetic modification, see the box on this page.)

The insertion of the Bt gene into maize was particularly significant for two reasons. First, approximately 7 percent of the world harvest is lost to the European corn borer each year. According to official estimates, one-half of the U.S. maize crop is infested with these borers and up to 30 percent of the crop can be lost every year, resulting in lost revenues of $1 billion. Second, neither Bt nor conventional sprays are particularly effective on maize once the larvae have bored into the stalks. By switching to Bt maize, farmers in the United States and Canada experienced average yield increases of 7 percent in 1997, and the application of artificial insecticides reportedly declined 30 percent in 1998 (though these claims have been challenged).[1]

Bt crops have been developed mainly by multinational companies that operate in several areas, such as pharmaceuticals, agricultural chemicals, and seeds. Some of these companies have recently expanded through mergers and acquisitions. Novartis, for instance, was created by the merger of two Swiss companies, Ciba-Geigy and Sandoz. AgrEvo resulted from the merger of two German companies, Hoechst and Schering, and subsequently acquired Plant Genetic Systems, a Belgium-based biotechnology company. And U.S.-based Monsanto has broadened its agricultural base by acquiring a number of seed companies. Through such actions, these firms are attempting to maximize their opportunities for inserting transgenes into existing crop varieties and capturing the market for genetically modified crops. All three are marketing varieties of Bt maize, which is being cultivated commercially in many countries, including the United States, Canada, Argentina, South Africa, France, and Spain.

To date, the regulatory debates over Bt maize have focused on two types of risk. The first is that the insecticidal gene might harm nontarget insects, including those that prey on the European corn borer itself. The second is the risk that the widespread use of Bt maize could lead to the prevalence of insects that are resistant to the toxin, thus jeopardizing the benefits of the product and perhaps undermining the efficacy of naturally occurring Bt for organic farming as well.

There has been much debate on ways to minimize or mitigate the selection pressure for resistant insects since the early 1990s. Some biotechnology companies are pursuing "genetic treadmill" solutions, attempting to develop new Bt toxins faster than insects can acquire resistance to them. As one company official proclaimed in 1991, "We have

The Ge

In this article, the term *genetic modification* refers to the insertion of an alien gene into a commercially valuable plant to give it useful new traits, such as a tolerance for herbicides or the ability to kill insects that feed on it. The gene in question may come from another plant, an animal, a virus, or a bacterium.

The process of genetically modifying a plant is relatively complex. The first step (1) is to extract a DNA sample from the organism containing the gene and to remove the gene by means of enzymatic "scissors." The second step (2) is to extract a plasmid (a circular fragment of DNA that replicates itself independently of an organism's chromosomal DNA) from the common bacterium *Escherichia coli* to serve as a vector for the gene of interest. The third step (3) is to open the plasmid and insert the gene of interest along with a "promoter" (another piece of DNA that will enable the gene to express itself) and a "marker" (an antibiotic-resistant gene that will enable technicians to isolate those cells in which the modification process has succeeded). The fourth step (4) is to place the modified plasmid into another bacterium (generally *E. coli*) and culture it to obtain more copies. The fifth step is to apply an antibiotic to the culture, killing all of the bacteria except those that have acquired the marker gene (and thus the gene of interest).

The final step is to insert the modified plasmid into the genome of the plant in question. There are two ways of doing this. The first (5a) is to extract the plasmids from their bacteria, place them on tiny (1 micrometer in diameter) pellets of tungsten, and shoot these pellets into cells from the plant. The gene of interest will become incorporated into the genome of some plant cells in a random fashion. The alternative (5b) is to transfer the plasmids to another bacterium, *Agrobacterium tumefaciens*, that is naturally able to introduce them into the genome of the plant and then culture the *A. tumefaciens* with the plant cells.

A major controversy has erupted over the use of antibiotic-resistant markers. In the case of a Bt maize developed by Ciba-Geigy (later Novartis), for instance, the marker is resistant to ampicillin, an antibiotic in the penicillin family. The company says that its use of this marker is perfectly safe because the ampicillin-resistant gene does not express itself in the plant, that is, the plant does not produce molecules that counteract ampicillin. Critics, however, claim that the gene could be transferred to bacteria in the stomach and intestines of humans, where it would be able to express itself. If so, this could lead to antibiotic-resistant strains of bacteria—and the possible loss of an effective drug.

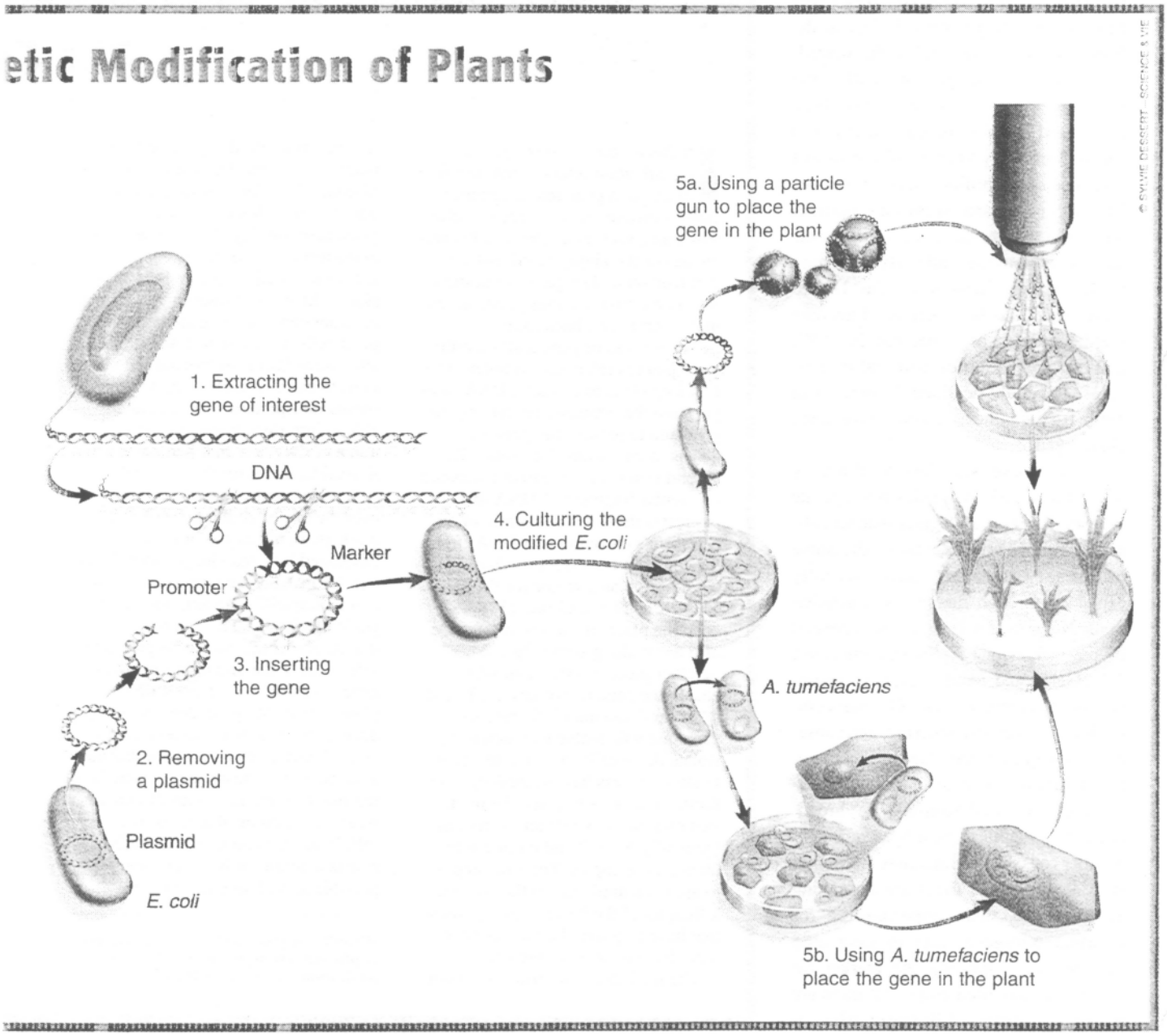
SOURCE: Adapted from "Plantes transgéniques: Le péril vert" (Transgenic plants: The green peril), *Science & Vie*, June 1999, 92–103.

many bullets in the gun which we call Bt."[2] Even if insect resistance were to develop in five years, the company would still receive an adequate return on its investment. In a similar vein, a report advised that insect resistance is unlikely to appear for at least five years, "when different and multiple enhanced sources of Bt and other toxins are planned for introduction."[3]

At the same time, companies have been devising strategies for insect resistance management (IRM), notably the "high-dose/refuge" strategy. In this strategy, the genetically modified crop is designed to produce enough of the toxin to kill nearly all resistant insects, while a nearby area of non-Bt plants allows some susceptible insects to survive and breed with resistant ones, thus diluting the resistance gene. (For more on insect resistance and its management, see the box on page 14.) As will be shown, such methods have been developed for somewhat different reasons in the United States and the EU.

U.S. Experience

In the United States, environmental organizations successfully pressured the Environmental Protection Agency (EPA) to regulate GM pesticidal toxins by extending its authority under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This act requires EPA to balance the risks against the benefits when approving new pest-control agents. EPA officials declared that genetically modified crops would significantly



reduce the risks associated with the use of artificial chemicals.[4]

However, the prospect of insect resistance undermined the longevity of the presumed benefits. In response to sustained political pressure, the agency eventually accepted the responsibility for preserving the efficacy of Bt as "a public good" through efforts to minimize insect resistance. This pressure succeeded because the emergence of insect resistance would create a real problem for farmers and the biotechnology companies alike.[5] Throughout all its policy shifts, EPA has claimed to base its decisions on "sound science," the practical meaning of which has changed in interpreting scientific evidence.[6]

Initial Controls

In 1995, EPA approved the GM toxin in three different Bt crops, on successively more stringent terms. For the first, a potato developed by Monsanto, no specific obligations were imposed on the company.[7] Monsanto, however, set its own guidelines for managing insect resistance while continuing research on better methods.[8] The company also included the IRM plan in its contracts with individual farmers.

In response, environmental nongovernmental organizations (NGOs) put out an "action alert" that was publicized by the magazine *Organic Farming*. As a result, EPA received several hundred letters criticizing it for prematurely allowing the commercialization of the potato and thus potentially compromising the effectiveness of Bt. This protest succeeded in influencing the agency's approach to subsequent applications for commercializing Bt maize and cotton: Applicants were required to monitor product use and to devise IRM strategies. EPA officials justified this more stringent approach on two grounds. The corn earworm is also the cotton bollworm, so the emergence of resistance in cornfields could affect cotton too; and EPA's conditions would provide credibility for the companies' efforts at product stewardship.[9]

In the case of Bt corn products devel-

Insect Resistance

The extent to which an insect population develops a resistance to the toxins produced by *Bacillus thuringiensis* (Bt) depends on a number of factors, most of which operate through genetic channels. Genes, the fundamental units of heredity, frequently have two or more variants known as *alleles* that occur at the same position on the chromosome where the gene is located.

The gene responsible for eye color in humans offers a familiar example. This gene has three alleles, which code for brown, blue, or green eyes. A person whose alleles are the same (e.g., brown-brown or blue-blue) is said to be *homozygous*; a person whose alleles are different (e.g., brown-blue) is said to be *heterozygous*. As is well known, the brown variant of the gene is *dominant*, the blue and green variants *recessive*. Any person who receives a brown allele from either parent (each parent contributes one allele to the new individual) will have brown eyes. To acquire a recessive trait such as blue eyes, a person must receive two recessive alleles (in this case, two blue ones).

Resistance to Bt toxins occurs when the insect produces proteins that block the sites at which the toxins would ordinarily "bind" or penetrate its molecular structure. According to the prevailing model, such resistance is a semirecessive trait, varying with the number of resistance alleles in the individual. Most individuals in an insect population are "homozygously susceptible" to Bt toxins, that is, they have two normal alleles and thus cannot survive exposure to Bt. By contrast, the few individuals that are "homozygously resistant" have two resistance alleles and so can tolerate a large dose of Bt. "Heterozygously resistant" individuals have an intermediate character—they can tolerate some exposure to Bt but cannot survive a large dose. However, individuals in this class can survive exposure if they learn to avoid crops that express high levels of Bt or if the Bt level declines toward the end of the growing season (as is the case with a Bt maize developed by Ciba-Geigy[1]). In the worst case, an individual may be resistant to more than one Bt toxin. This is apt to occur when the proteins that confer resistance block the same binding sites of the toxin and/or different toxins have the same binding site.[2]

The survival of homo- or heterozygously resistant individuals enables them to pass the resistance alleles on to the next generation. How widespread the trait becomes depends on several factors, including the initial frequency of resistance alleles; the degree of "selection pressure" (i.e., the number of resistant individuals that survive all causes of mortality and are able to mate); and the number of binding sites of the toxin. It also depends greatly on the percentage of susceptible individuals in the nearby population. The higher that percentage, the higher the probability that a resistant individual will mate with a susceptible one and the lower the probability that the semirecessive resistance trait will be passed on. This is the reason that insect resistance management often relies on structured refuges, untreated crops that support a pool of susceptible insects.

The refuge strategy depends on Bt resistance being a semirecessive trait. However, recent research indicates that it may be dominant, that is, that heterozygously resistant individuals can tolerate high doses.[3] If such dominance exists in field populations, refuges may do little to delay resistance.

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1. Ciba-Geigy, "Application for Placing on the Market a Genetically Modified Plant (Maize Protecting Itself against Corn Borers), Directive 90/220/EC," Part C, Notification C/F/94/11-03, 1994.

2. For this reason, the biotechnology companies have developed Bt crops with toxins that bind to different sites. See AgrEvo USA, *New StarLink: The Next Generation of Bt Corn* (Apple Valley, Minn., 1998); and Novartis Seeds, *Erase Corn Borer Problems with NK Brand Bt Hybrids: 1998 Grower Guide* (Minneapolis, Minn., 1998).

3. F. Huang et al., "Inheritance of Resistance to Bt Toxin (Dipel ES) in the European Corn Borer," *Science* 284 (7 May 1999): 965–66.

oped by Ciba-Geigy and Mycogen, EPA did not expect these crops to dominate the market in the early years, when there would be natural non-Bt refuges between fields; therefore, "market-driven unstructured refuges" would be adequate to delay resistance. But EPA did require some IRM measures to preserve the efficacy of Bt sprays as well as that of the Bt crop itself. These IRM plans would require "close monitoring of the plant pesticide to determine if resistance is developing," i.e., if there were any surviving pests. The company would then test them for increased resistance and, if that was found, implement a refuge strategy.[10] According to regulators, the companies' plans would reduce the possibility of resistance developing for three to five years.[11]

EPA also granted conditional approval to a Bt cotton developed by Monsanto. The plants were expected to produce a sufficiently high dose of the toxin to kill all the insect pests, thus creating no selection pressure for resistant ones. Just in case, however, each field would include refuges of non-Bt plants so that some susceptible insects would survive and breed with resistant ones. Refuges had to cover 4 percent of the cultivated area, or 20 percent if the crop was sprayed with a chemical insecticide.[12] Thus, the IRM plan called for changes in seed marketing and field cultivation.

Precautionary Limits

Some EPA staff were ambivalent about what could be achieved through resistance-management strategies. They were aware that field inspectors are trained mainly to detect harm to nontarget species rather than the presence of resistant insects, whose survival would be difficult to interpret in any case.[13] Other officials acknowledged the inherent limits of such strategies: "We have made an agreement to implement 'reasonable measures' to minimize the development of resistant insects—not to prevent their development, which is taken as a given for Bt crops," said one U.S. Department of Agriculture (USDA) official who was working with EPA on these efforts.[14]

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A test plot of wheat that has been genetically modified to be resistant to the chemical herbicide Avadex.

For their part, some industry officials argued that IRM strategies should remain voluntary, i.e., as part of the companies' product stewardship programs.[15] They questioned whether FIFRA gave EPA the authority to regulate Bt resistance according to a public-good criterion.[16] Others, however, appreciated the government's role in accommodating protest: Although it was cumbersome for a company to submit annual monitoring plans to EPA, such a requirement could help it deal with public concerns.[17]

Implementation of resistance-management strategies was the main demand made by environmental NGOs. Organic farming advocates also put pressure on the government at USDA's national forum on Bt resistance in 1996.[18] According to one NGO, "the three Bt resistance plans basically represent large-scale experiments on an unproven but promising strategy."[19] According to these critics, EPA was simply assuming that Bt crops would reduce chemical usage; in their view, the agency had optimistically accepted the high-dose/refuge strategy while ultimately looking to a genetic treadmill solution.[20] To highlight the need for caution, these groups publicized the expert arguments about the limitations of IRM strategies.[21] Then, in September 1997, a coalition of environmental NGOs accused EPA of gross negligence on several grounds—notably that the agency had not proven the safety of the Bt crops before registering them and that they threatened organic agriculture.[22]

Mishaps with Bt crops soon reinforced doubts about their long-term benefits. In July 1996, Monsanto's Bt cotton succumbed to bollworm in some southern states. Because the IRM plan had presumed that a high dose would kill virtually all the pests, critics questioned whether it was adequate to delay resistance.[23] However, a leading entomologist argued that the bollworm is less sensitive to the Bt toxin than are other pests, "so it is misleading to use this cotton in a high-dose/refuge approach."[24] In August, EPA restricted the cultivation of Bt maize in the South on the ground that it could lead to resistance in the corn earworm, which is also the cotton bollworm.

The adequacy of IRM strategies was challenged by further evidence. According to some scientists, Bt resistance may not always be a semirecessive trait; if it is dominant, it could spread more rapidly in target insects than previously thought.[25] In addition, some insect pests were found to have single genes that confer resistance to four different types of Bt.[26] In view of this, experts questioned the utility of substituting alterna-

tive Bt genes if the insects developed resistance to the initial one.

According to some experts, an insect with a high background level of resistance genes may develop considerable resistance to the Bt toxin in three to four years even with a refuge strategy.[27] According to other experts, the rate at which resistance develops depends less on the background level of resistance genes than it does on the survival rate of heterozygously resistant insects.[28] That possibility makes it all the more necessary to ensure the efficacy of the high-dose/refuge strategy.

In response to these concerns, EPA's Scientific Advisory Panel emphasized the difficulties of IRM strategies: "There is disagreement as to . . . the necessary arrangement and relative size of Bt and refuge field plots [as well as to] the nature and objective of performance-monitoring activities."[29]

In 1998, the Union of Concerned Scientists published a report in which some of the same experts made specific recommendations for tightening the IRM strategies. The group added its own warning: "Immediate action is required because U.S. agriculture is already 3 years into what has become a multimillion acre experiment on resistance development and transgenic crops." Criticizing intensive monoculture, it reiterated previous calls for a shift to multiyear rotations that would minimize the need for pesticides: "To the extent that Bt crops further entrench the present system, they impede that important transition."[30]

Tighter IRM

In May 1998, EPA's Scientific Advisory Panel recommended stricter requirements for refuges. To delay insect resistance, whose risk is "real," EPA should "require the use of structured refuges," i.e., with specified patterns, sizes, and proximity to the Bt crop. A "sustainable approach" would be necessary to protect "this very valuable and environmentally friendly technology." According to the panel, the requirements should be even stricter for those crops that do not maintain high Bt levels throughout the growing season, such as Ciba-Geigy's first Bt maize.[31]

Heeding that advice, EPA tightened its controls in granting two further authorizations for Bt maize. Under the earlier approvals, the agency had accepted the adequacy of unstructured refuges (whose sizes were determined largely by market conditions) because most farmers had not yet adopted Bt crops. Now EPA mandated that non-Bt refuges cover 20 to 30 percent of the cultivated area, or 40 percent if sprayed with insecticide. In setting these requirements, the agency again cited the need to preserve the efficacy of Bt sprays as well as that of the Bt crop itself.[32]

The debate in Europe has focused on indirect harm to carnivorous insects higher in the food chain.

Soon the larger refuges were being promoted by some companies,[33] though there were differences among the four competing to sell Bt maize. In 1998, all four participated in an expert panel that devised a "science-based framework" for managing insect resistance to Bt. Their report specified refuge sizes that in some cases were larger than those in previously mandated plans.[34] Farmers would also be required to sign contracts undertaking to follow the guidelines. These arrangements were intended to avoid several potential problems: differences among the four companies, confusion among farmers, and more stringent EPA requirements. The guidelines were endorsed by the National Corn Growers' Association.[35]

The IRM measures entailed a real (and ongoing) dilemma. To prolong the environmental benefit of Bt crops, EPA made the controls more stringent, but this limited the short-term benefit and appeal of such crops to farmers. At the same time, the agency remained uncertain how effective the controls would be in delaying insect resistance, and its staff had no clear way to know whether or why some pests survive.

European Experience

In 1990, the European Community issued Directive 90/220 on the Deliberate Release to the Environment of Genetically Modified Organisms.[36] This was intended to "establish harmonized procedures and criteria" for Europe-wide market approval of genetically modified products. Although the directive was called "preventive," the term implicitly meant "precautionary." Reaffirming the directive, a later document established the "precautionary principle" as EU policy.[37]

The approval of genetically modified crops has encountered more criticism since the European Community was expanded into the European Union in 1995. New member states—Sweden, Finland, and Austria—joined Denmark in advocating a broader definition of the "adverse effects" that must be prevented under the directive.[38] By the late 1990s, even more member states had broadened such definitions and strengthened the burden of evidence for safety. Some have come up with their own safety plans, going well beyond the EU statutory basis.[39] As the agency responsible for Directive 90/220, Directorate General (DG) XI for Environmental Protection has sought to mediate the disagreements among member states.

Ciba/Novartis's Maize: The Test Case

The first test case for commercial cultivation arose in 1994, when Ciba-Geigy

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A protester in "protective" clothing uprooting genetically modified plants in the United Kingdom.

submitted a marketing application for a Bt maize to French authorities, thereby making France the rapporteur for the EU-wide procedure.[40] Member states raised questions not only about the Bt gene but also about the two "markers" used, one of which conferred tolerance of herbicides and the other resistance to the antibiotic ampicillin. Despite objections from most countries, the European Commission approved the application. In doing so, it accepted the French authorities' judgment that the emergence of insect resistance "cannot be considered an adverse environmental effect, as existing agricultural means of controlling such resistant species of insects will still be available."[41] Insect resistance was deemed an agricultural problem, not an environmental threat. In effect, the biopesticide Bt would be dispensible, ultimately replaceable by artificial insecticides.

After gaining EU-wide approval, the product encountered further delays under the National List procedure, which requires registration for any new crop variety.[42] By then, there was an intense public controversy in France over genetically modified crops. Numerous scientists, environmental NGOs, and the peasants' confederation were demanding a complete moratorium on all commercial use of such crops.

After a long delay, the French government finally registered Ciba-Geigy's maize in February 1998. The registration was unusual, however, in only being for three years and in requiring monitoring for various environmental effects, including the efficacy of the Bt toxin, insects' resistance to it, harm to non-target insects, its effects on other organisms, and the spread of the ampicillin-resistance gene.[43] In its National List procedure, Spain imposed similar requirements on Ciba-Geigy's Bt maize along with a general monitoring requirement for all genetically modified crops listed in the future.[44]

Another controversial aspect was the possibility that the ampicillin-resistant marker could lead to the emergence of bacteria impervious to this antibiotic, thus undermining its clinical efficacy. Ciba-Geigy's risk assessment barely mentioned the presence of this marker, and the French authorities asked no questions about it. (Nor, for that matter, had the U.S. Food and Drug Administration when it approved the product.) Only in the EU-wide procedure did objections arise—from NGOs and some other member states. In response to these concerns, EU-level scientific committees evaluated the marker gene and concluded that it was safe.[45] In late 1998, the issue came back full circle to France when its constitutional court declared that the product approval was invalid because the evaluation procedure had failed to assess the ampicillin-resistance gene. This ruling precluded further cultivation of the Ciba-Geigy/Novartis maize in France and intensified the political uncertainty about GM crops across Europe.

Shortly after its approval in early 1997, moreover, Ciba-Geigy's Bt maize was banned in Luxembourg and Austria, where genetically modified crops symbolized an environmental and commercial threat to organic agriculture. When the European Commission sought to remove these bans, only a few member states supported it so the bans stayed in place. In addition, some countries used the occasion to pressure the commission to assume responsibility for evaluating companies' plans for IRM.

IRM Plans Evaluated

Even before Bt crops were approved for cultivation, the seed companies had committed themselves to minimizing the selection pressure for resistant insects. Ciba-Geigy made such a commitment in a 1995 letter to DG XI during the Directive 90/220 approval procedure. Monsanto did so in its 1995 marketing application for Bt maize.[46] Under pressure from various sources, DG XI asked the EU-level Scientific Committee on Plants to evaluate these IRM plans. The committee concluded that they would be "adequate to delay resistance," while implying that such an effect would be an agricultural problem rather than an "adverse effect" under Directive 90/220.[47]

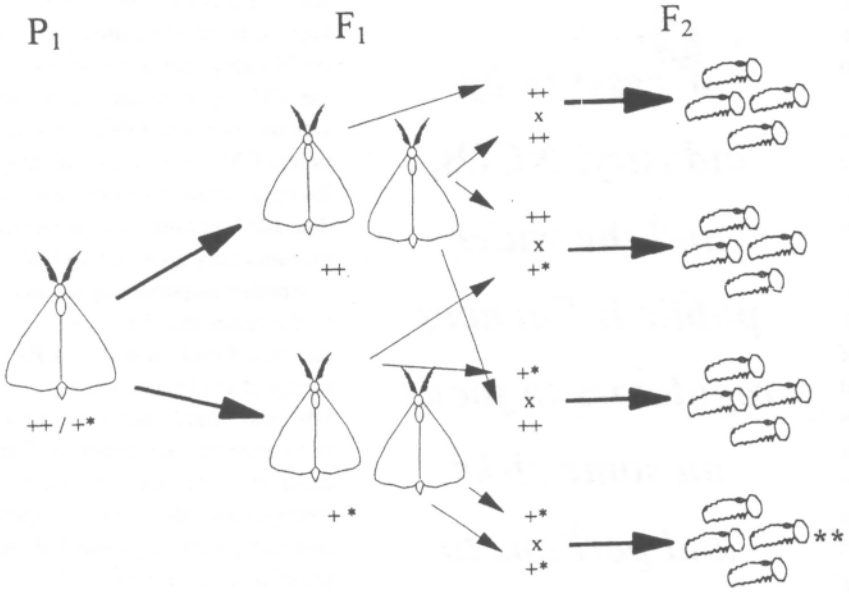
Another EU-level expert group discussed a methodological difficulty, namely, the fact that resistance genes may be widespread in the population by the time any resistant insects are detected. The simplest approach would be for farmers to look for any abnormal crop damage or surviving insects, the latter of which would then be tested in the laboratory. However, some member states regarded this method as inadequate and demanded "active," systematic monitoring.

Entomologists have developed methods for sampling and testing insect populations to detect any increase in heterozygously resistant individuals. The most sophisticated method is similar to one devised in the United States (see Figure 1 on this page).[48] After four generations in the field, insect samples would be tested in the laboratory at various doses. After eight generations, new samples would be interbred over several generations and tested at progressively higher doses. The inbreeding would concentrate any resistance alleles in the subsequent generation, thus simulating the development of homozygously resistant insects. With these standard laboratory tests for Bt susceptibility, baseline levels could be measured and then compared over time and across environments. Testing would be done more frequently for the Mediterranean corn borer than for the European corn borer, which has fewer generations per year.[49]

Because meaningful lab testing depends on knowing the previous level of Bt susceptibility in the insect population, Novartis contracted with entomologists at the University of Milan to establish a baseline. And as the refuge design depends on assumptions about the distance traveled by insects to feed and breed, biotechnology companies have also contracted with entomologists to study these behaviors.

To create refuges that would minimize selection pressure, Novartis originally planned to follow the early EPA guidelines but later adopted that agency's more stringent ones. To implement its strategy, Novartis offered farmers a financial incentive. In the words of one company official, "[g]rowers who buy a significant amount of Bt seed receive substantial savings if at least 20 percent of their order includes non-Bt hybrids. With this program, Novartis Seeds is offering to share IRM stewardship responsibilities with its customers."[50] Because little Bt maize was cultivated in France in 1998, the refuge protocol was probably fulfilled by nearby non-Bt crops in any case.

Figure 1. The F_2 screen for detecting insect resistance



NOTE: This figure illustrates a technique developed to detect the emergence of resistance to the Bt toxin in the European corn borer at an early stage, i.e., before resistant individuals become apparent in the field. The technique consists of breeding (in the laboratory) two successive generations within a single female line to concentrate the resistance alleles; observing the number of homozygously resistant individuals that results; and then using statistical techniques to infer the prevalence of such individuals in the wild. The P_1 generation consists of impregnated females captured in the field. Their offspring, the F_1 generation, are interbred with their siblings to produce the F_2 generation. As the figure shows, given a cross between a homozygously susceptible parent (++) and a heterozygously resistant parent (+*) in the P_1 generation, one would expect 1-16th of the larvae in the F_2 generation to be homozygously resistant (**). If no such individuals are found in 1,200 family lines, one can conclude with 95 percent confidence that the initial frequency of resistance alleles in the sample population is less than 1 in 1,000. Similar inferences can be made for whatever number of homozygously resistant individuals are found. Moreover, those individuals can be studied at greater length in order to make realistic predictions as to the evolution of resistance.

SOURCE: D. A. Andow and D. N. Alstad, "F_2 Screen for Rare Resistance Alleles," *Journal of Economic Entomology* 91, no. 3 (1998): 572–78. Used with permission. See also M. Mellon and J. Rissler, *Now or Never: Serious New Plans to Save a Natural Pest Control* (Cambridge, Mass.: Union of Concerned Scientists, 1998), 45–46.

Nontarget Harm Disputed

Potential harm to nontarget insects also became an issue early in the European regulatory procedure. Before the first Bt crops gained EU approval, several insect species underwent laboratory tests using microbial Bt. They showed no evidence of harm, according to Monsanto.[51] Critics, however, proposed that the company redo the tests with more insect species and using Bt derived from the genetically modified plant instead of from Bt microbes, because the former could have different effects. Monsanto claimed that enormous quantities of the plant would be

needed to extract a high enough dose.[52] More recent tests have used either plant-produced Bt or microbe-derived Bt of the same type that is inserted into crops. In addition, field surveys monitoring potential harm found just as many beneficial insects in Bt-crop fields as in non-Bt fields.[53]

Recently, the debate in Europe has focused on indirect harm to carnivorous insects higher in the food chain, such as the lacewing, a beneficial predator commonly found in maize fields. In a laboratory experiment in Switzerland, lacewing larvae that ate Bt-fed corn borers had a lower survival rate or developed more slowly than those that ate non-Bt corn borers. Similar harm was found when using an alternative species as prey.

The Swiss researchers suggest that the reduced fitness was associated with the Bt toxin and that the prolonged development time was caused by both the exposure to Bt and a nutritional deficiency from eating sick prey. If this were to happen in Bt maize fields, they argued, farmers would lose a useful means of controlling Bt-resistant insects.[54] That study was cited by environmental NGOs and Austrian officials as grounds for banning the product. Scientists further debated appropriate methods for testing indirect harm in lab and field studies, yet the potential link to IRM was largely ignored in the public debate.

In light of the Swiss study, the Scientific Committee on Plants was asked to evaluate the probability of harm to non-target insects. In the committee's judgment, any such harm would be less than that currently caused by chemical insecticides.[55] In other words, the committee accepted the present effects of chemical-intensive agriculture as the normative baseline for the potential effects of genetically modified crops—even though not all maize is sprayed with chemical insecticides. This led to further debate over the appropriate reference point for genetically modified crops.

Such arguments were intensified by U.S. research indicating that genetically modified maize pollen harms Monarch butterfly larvae.[56] In response, the European Commission delayed approval of a genetically modified maize from Pioneer Hi-Bred in mid-1999. Thus, any evidence of risk could serve to strengthen the regulatory blockage of Bt maize.

A Scientific-Cultural Comparison

Although there are some similarities in the ways in which the United States and the European Union have handled Bt maize, the differences are much more pronounced. One significant difference pertains to the responsibility taken by regulators. The U.S. Environmental Protection Agency originally had no clear authority to regulate genetically modified crops; nonetheless, it eventually assumed the responsibility for regulating plant pesticides in general as well as for managing insect resistance in particular. The latter policy was a response to pressure from environmental NGOs, organic farmers, entomologists, and others who stressed the need to preserve Bt as a public good.

Pressure by industry, NGOs, and the wider public influences regulators to focus on some risks and perhaps to downplay others.

The EU, by contrast, has had the statutory authority to regulate all the risks associated with genetically modified organisms since 1990. Nonetheless, EU-wide product approvals have avoided responsibility for managing insect resistance, though DG XI provided relevant scientific advice. Individual member states have acted to fill the regulatory gap, e.g., through regulatory delays and extra controls.

Although the IRM strategies adopted by the United States and the EU are broadly similar, they came about in response to very different pressures. In the United States, insect resistance was the principal concern raised about Bt crops—as an issue related to maximizing the benefits of such crops. A broad alliance emphasized that such resistance was a plausible risk in the context of large-scale maize cultivation, a risk that could easily spread to cotton as well. In the EU, by contrast, insect resistance was one of several risks cited in opposition to GM crops in general. In response, European regulators have sought to validate IRM measures to demonstrate their precautionary approach to GM crops.

Another important difference pertains to the harm that Bt maize could inflict on beneficial insects. EPA simply accepted the biotechnology companies' lab and field studies showing no occurence of such harm. In Europe, by contrast, scientists' evidence of risk strengthened the overall argument for banning genetically modified crops. The possibility that the ampicillin-resistance gene could undermine the clinical efficacy of that antibiotic has also been contentious. This risk was simply ignored by U.S. regulators and most NGOs in the United States. In Europe, on the other hand, it was the subject of a fierce debate. Indeed, antibiotic resistance became a major issue in the European regulatory procedure, prompting widespread arguments for a moratorium and a French court decision revoking the license for a Bt maize product already in commercial use.

Understanding the Differences

U.S.-EU differences in regulating Bt maize stem partly from their different geopolitical contexts (see Table 1 on page 20). U.S. regulators have faced stronger political pressures to permit

Table 1. Regulatory contexts and criteria for Bt maize

	United States	European Union
Context:		
Agricultural policy/trend	Low-cost, high-volume production for export	High-quality production
Maize trade	Large net exporter	Net importer, especially from the United States
Microbial Bt sprays	Used extensively on cotton, somewhat on maize	Rarely used on cotton or maize
Proximity of cotton crops to maize crops	Often grown in close proximity; corn earworm (same as European corn borer) infests both crops	Rarely grown in close proximity
Maize pests	European corn borer	European corn borer, Mediterranean corn borer
Focus of public debate	IRM methods, scientific issues; demand to preserve Bt	Various risks from genetically modified crops; general demand for moratorium
Organized protest	Informal alliance including organic farmers	Loose network of diverse groups
Regulatory policy:		
Regulatory authority	EPA for Bt risks; USDA for other crop risks; FDA for food and feed risks	Directorate General XI for all risks
Precautionary principle	Implicit in EPA decisions	Explicit policy, with diverse accounts
Commercialization of Bt maize	Several varieties cultivated on a large scale	Blocked or delayed despite EU approval
Ampicillin-resistance marker in Ciba-Geigy's maize	FDA raised no questions	Rapporteur (France) raised no questions but other authorities did
Regulatory norm for insect resistance	Preserve Bt as a public good	EU treats Bt as dispensable but member states have enacted regulations
Harm to nontarget insects	Accepted evidence of safety with little debate	EU accepted possibility of harm, member states have enacted regulations
Market-stage monitoring	Tightened requirements for reporting on insect resistance	Quasi-voluntary IRM monitoring at the EU level, mandatory monitoring for all risks in France and Spain
Cultivation protocol	Tightened requirements for products approved in 1998	No formal requirements, but EU experts have evaluated company plans

SOURCE: Les Levidow.

commercialization as well as a more plausible risk that insects would develop resistance to the Bt toxin. As a result, the threat of insect resistance was the main lever available to NGOs concerned that GM crops would aggravate the problems of intensive monoculture. In Europe, by contrast, more broadly based public opposition pushed regulators to take a generally precautionary approach to Bt maize. In addition, harm to nontarget insects seemed more consequential in a region where farms tend to be smaller and in closer proximity to wildlife habitats than they are in the United States.

As a deeper source of the differences in regulatory approach, agriculture has different cultural meanings in the two regions. U.S. farms are seen as analogous to factories and are sharply demarcated from wilderness and nature conservation areas. Although European agriculture also uses chemical-intensive methods, it is widely regarded as an integral part of the environment, i.e., as an aesthetic landscape, an element of local heritage, and wildlife habitat. This cultural difference has been accentuated by a recent divergence in agricultural policy. The U.S. government has reduced price supports for agriculture, pressed other countries to do likewise, and actively promoted biotechnology through such measures as extended patent protection. These policies were in response to pressure from multinational companies, which have sought to enhance the market for high-productivity agricultural inputs (such as genetically modified seeds), to drive down the price of bulk food commodities, and to obtain multiple sources of inputs for the global food processing industry.[57]

By contrast, the EU has been moving towards less-intensive, higher-quality production that favors greater caution towards biotechnology.[58] That tendency has been reinforced by the 1996 crisis over "mad cow disease," which has undermined public confidence in food regulation and aroused suspicion toward any claims for more efficient food production, especially from biotechnology. When Monsanto's herbicide-tolerant soybean began to appear in processed

foods in 1997, public protest mounted against all genetically modified crops and food, leading to widespread demands for a moratorium.

These U.S.-EU regulatory differences also highlight the contingent role of science in environmental protection. Risk regulation entails judgments about what "environment" must be protected, what uncertainties matter for risk assessment, and what research could clarify them. At issue is the interpretation of scientific data and even the questions that research should address. As a result, the precautionary principle is necessarily redefined anew in each context.

Although Bt maize poses various risks, the relative plausibility of those risks does not explain policy responses. Rather, pressure by industry, NGOs, and the wider public influences regulators to focus on some risks and perhaps to downplay others. Such emphases are inherently cultural, irreducible to a single, objective basis. For this reason, purely "science-based regulation" can never be achieved.

When European regulators delay or restrict the commercialization of genetically modified crops, they are criticized for basing their decisions on politics rather than science, yet such a distinction is misleading. Approvals of those crops are no less political in their judgments about the acceptability and predictability of potential harm. As technical criteria are subjected to further public debate, the legitimacy of commercialization will depend on extending the precautionary measures and holding decision makers publicly accountable.

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NOTES

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3. James, note 1 above, page 31.

4. R. Hoyle, "EPA Okays First Pesticidal Transgenic Plants," *Nature Biotechnology* 13 (1995): 434–35.

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14. Official at the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, interview with the author, 18 June 1996.

15. Official at the Bio-Industry Organization, interview with the author, 18 October 1995.

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17. Official at Novartis, interview with the author, 27 January 1998.

18. J. Fox, "Bt Cotton Infestations Renew Resistance Concerns," *Nature Biotechnology* 14 (1996): 1,070.

19. Hoyle, note 4 above.

20. Official at the Environmental Defense Fund, interview with the author, 27 October 1995.

21. See issues of *Gene Exchange* published in 1997–98.

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