Bt
a
short
history
of
Bacillus thuringiensis

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This study is based on a report that was partly financed by DG XII of the European Commission as Project BIO4-ct97-2363. The analysis and conclusions are those of the authors and do not reflect the views of the Commission.

November 1999

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November 1999

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"It is humbling and instructive that the most exquisitely specific group of insecticides known originates not from a laboratory, but instead from the common soil bacterium Bacillus thuringiensis. Insecticidal crystal proteins produced by Bt kill insects by binding to and disrupting their midgut membranes. Each of the numerous strains of Bt produces a characteristic set of crystal proteins. Each of these toxins is lethal to certain insects, yet does little or no harm to most other organisms, including people, wildlife and even other insects."
Bruce Tabashnik
Department of Entomology
University of Arizona
1997

1. INTRODUCTION

Most plant varieties have the ability to resist pests and disease. The mechanisms of resistance can be varied, including structural characteristics of the plant, the production of general metabolites that have toxic properties, or the production of specific toxic substances in response to pest attack. A plant can be completely immune to a pest or it can be partially resistant.

Plant varieties with a greater ability to withstand pests have traditionally been bred from progenitor plants that have high levels of resistance to the target pest. It is now also possible to introduce mechanisms of pest and disease resistance into plants that are not found in the plant kingdom. For example, plants can be genetically engineered to express toxins from invertebrates and microorganisms. These toxins can confer plant resistance to insect attack and disease. Such pesticidal substances can be diverse and can potentially originate from any taxonomic kingdom.

There are a number of types of substances produced in plants that enable plants to resist pest attack and disease. These substances include both those pesticidal substances that would be considered normally a component of a plant and those that would be considered new to a plant. Examples of plant-pesticides that would be considered normally a component of a plant are phytoalexins (plant-produced substances that act against phytopathogenic microorganisms). An example of a plant-pesticide that would not be considered normally a component of a plant is the insecticidal delta endotoxin that is produced in the bacterium, Bacillus thuringiensis.

A range of genetically engineered biopesticides, including pest-resistant plants are currently being developed by the life sciences industry. According to the industry, these biopesticides promise to replace chemical pesticides and thereby reduce the environmental problems associated with the use of certain agro-chemicals over the past 50 years. The industry also claims that biopesticides might be cheaper and easier to use than their chemical counterparts, especially when the toxin is incorporated into the actual plant. There are, however, problems concerning the longer-term biological efficacy of all biopesticides, just as there are with chemical pesticides. Pests are known to develop resistance to all types of pesticides and unless the dynamics of this process are properly studied and understood, *and* the use of pesticides in the field is actually informed by this knowledge and properly controlled, the new biopestides will join their chemical counterparts on the pesticide treadmill, where the industry has to keep inventing new poisons simply in order to maintain the status quo.

This outcome is not necessarily contrary to the commercial interests of the life industry and can indeed be economically beneficial to the companies concerned. However, the development of pest resistance to biopesticides will have damaging long term consequences for organic agriculture, the development of sustainable agriculture and low-risk food security programmes. The irresponsible commercialisation of biopestides could also cause irreversible changes in the biosphere. Bt occurs naturally as a soil bacterium throughout the world. Its role in natural ecosystems has not been studied in any detail and remains a mystery but it must be presumed that certain insect populations are naturally reduced or controlled by the presence of Bt. If these insects develop immunity to Bt they will, accordingly, become more abundant. The insects happen to include a number of major crop pests.

Just fifteen years ago, it would have been technically and biologically possible to develop a range of biopestides that would not only have replaced their environmentally damaging chemical equivalents, but could have been used in a sophisticated and sustainable way for the foreseeable future. Bt was the prime candidate for this role but its potential has been all but destroyed by a handful of companies motivated only by short-term economic goals.

This report documents the disaster in order to learn from it, in the hope that the same sorry history is not now repeated with Photorhabdus luminescens (PhL), the bacterium that is now being touted around by the genetic engineering industry as the new wonder biopesticide that will replace Bt.

There was no shortage of warnings from scientists, farmers and environmental activists concerning the fate of Bt. In fact the short, disastrous history of the commercialisation of Bt was entirely predictable.

US Environmental Defence Fund

Nearly eleven years ago, on 9th January 1989, Rebecca Goldberg from the Environmental Defence Fund wrote as follows to the US Environmental Protection Agency:

"Decisions about regulatory policies are often best made a priori rather than in the pressured atmosphere accompanying agency decision-making about particular products......Resistance to chemical pesticides is a pressing problem that continues to grow. Thus it is reasonable to ask whether pests will also evolve resistance to organisms genetically engineered to control them.....The most immediate concern is the evolution of resistance to delta-endotoxins from Bacillus thuringiensis. Bt toxins are environmentally benign compared to most other pesticides and Bt toxin genes are being engineered into a number of plants and bacteria. The evolution of resistance to Bt toxins would jeopardise further use of these genes, and thus the adoption of alternatives to conventional chemical pesticides"

Rural Advancement Fund International

A couple of months later, Hope Shand of the Rural Advancement Fund International wrote an article on Bt in the Journal of Pesticide Reform Vol 9 No 1 pp 18-21 Spring 1989

"If insecticidal Bt genes are widely introduced in commercial, homogeneous cultivars, pests will adapt to them and this valuable natural resource will be squandered. A safe and effective biological insecticide could be rendered ineffective and potentially damaging because of over-use or mis-use. Ironically, agriculture could bee pushed back to even greater reliance on conventional pesticides."

NovoNordisk 1992
The Danish biotechnology company which invested heavily in the breeding of Bt strains for traditional external use in the 1980s sounded a note of caution regarding the development of Bt plants in 1992 and decided to sell off all its Bt interests in 1994.

"The successful use of new Bt-based biotechnology products depends on the development and implementation of sound management strategies. In the past, resistance management to chemical insecticides has occurred after resistance reached crisis proportions. With current Bt products, resistance has developed in fields under continuous, intensive use of new Bt-based biotechnology products.....As new biotechnology products based on Bt are developed, the challenge to use these products in a sound manner that maximises their field life becomes critical. Pest control specialists view resistance as the single most important issue in the development of single gene Bt-based products such as single gene transgenic plants. We now have the opportunity to demonstrate the lessons of past use of chemical insecticides by developing sound strategies for using Bt-based biotechnology products in pest management systems in advance of their actual commercialisation and marketing."

Nature
In 1993, Robert May, from the Department of Zoology at the University of Oxford wrote an article in Nature warning that genetically engineered Bt crops could quickly become useless.

"In the heady years after the Second World War it briefly seemed as if DDT and other pesticides would win the age-old human war on insect crop pests and disease vectors. Such dreams overlooked the way the natural world has been shaped by evolutionary challenges and responses - the challenge of chemical pesticides soon evoked a response of resistant genotypes of arthropods. Today, more than 500 species of insects and mites that are pests in crops and orchards have evolved resistance, often to a wide range of different pesticides. Overall, more than one-third of all agricultural production is lost to pests, the same proportion as a century ago. Now a new battle-line is about to be drawn - genetically engineered crops that contain insecticidal toxins will soon be available commercially. But the usefulness of such transgenic crops will be short-lived if insects quickly adapt to the toxins."

Bioworld Today
The editorial in Bioworld Today dated 20 May 1994 drew attention to the widespread myth that insects could not develop immunity to Bt.

"In the never-ending war between farmers and insects the ultimate weapon on the human side is a protein produced by a soil bacterium, Bacillus thuringiensis - Bt for short. Like DDT in decades past, Bt puts down a very wide range of crop pests, but unlike DDT it is environmentally correct, harmless to humans, and apparently defies anti-Bt resistance developed in the insect enemy. Apparently, but not really. Some years ago, watercress growers in Hawaii found that the diamondback moth, which feeds exclusively on cruciform plants - cress, cabbage, cauliflower and the like, was munching on the watercress crop with impunity, even though its leaves had been sprayed with Bt."

New Scientist
The editorial in the New Scientist dated 8 March 1997 accused the genetic engineering industry of irresponsibility.

"It is always a tragedy when a gift from nature is squandered, whether it is a river dead from pollution or a forest laid waste for timber. Lets hope that the biotechnology industry is not about to throw away the enormous potential of a simple bacterium, Bacillus thuringiensis, in its haste to get to market. Properly used, the bacterium could provide a wonderful way to control insect pests and help farmers to gain high yields without synthetic pesticides. Misused, however, and pests will grow resistant to it and its power will be gone for good. Over-eager gene cloners are already rushing in where cautious ecologists fear to tread. The latest research suggests that its time to slow them down."

1.1. Pest Control Methods

There is nothing new about biological, as opposed to chemical methods for controlling pests. Farmers have used biological methods for the control of pests for generations. In the broadest use of the term, traditional biopesticides control pests by using their natural enemies. More recently it has proved possible to breed or engineer biopesticides for specific purposes.

There are a number of problems with current methods of dealing with agricultural pests:

(a) an increasing need for pest control measures resulting from more and more genetically homogeneous monocultures and an increasing regional division of labour for particular crops which maximise the vectors for the multiplication of pests
(b) increasing environmental problems resulting from the use of agrochemicals - especially water quality
(c) public concern about the implications of agrochemicals for human health - especially agrochemical residues in food

Various solutions have been proposed and are currently being trialed in the field :

(a) integrated pest management (IPM), which involves monitoring and targeting pests in order to reduce agrochemical use by encouraging the specific rather than the routine use of chemical pesticides

(b) integrated crop management (ICM), which aims to reduce pest invasions by planning the juxtaposition of crops and rotations to reduce the vectors for the multiplication of pests

(c) organic agriculture (ORG), which aims to reduce pest invasions using a number of approaches, including increasing the biodiversity of farms (thus minimising the vectors for the multiplication and mobility of pests), companion planting/polycultures, the introduction of pest predators ranging from bacteria to insects, "natural" poisons such as nicotine, and when all else fails, manual control

(d) genetic engineering (GE), which is currently transferring naturally occurring poison-coding genes from bacteria into crops

There is no clear dividing line between any of the four methods of controlling pests described above and to one extent or another, they all face the same systematic biological problem - that pests can develop resistance to chemical and biological pesticides through genetic mutations.

The "ideal" pesticide would be environmentally safe and biologically effective - indefinitely. However, a combination of natural selection and the workings of the market make a mockery of this ideal. Generally speaking, the more biologically effective a pesticide, the more it is used and the quicker the pest becomes resistant. For effective, long-term use, it is thus important both to use and NOT use a pesticide. If pests are not provided with a refuge, we maximise the biological advantage of those individual pests with mutated genetic resistance so that they soon dominate the total population. This is especially the case with insect pests that breed many generations in a single growing season.

No pesticide is effective *per se,* and all pesticides are probably doomed to become more or less totally ineffective if we continue to grow our food in the form of spatial monocultures dominating whole landscapes, and temporal monocultures that never rotate crops from one year to the next. The efficacy and fate of a pesticide is thus determined to a large extent by the way it is used. This is acknowledged in the EU pesticide regulatory legislation, which makes it necessary to report resistance to any pesticide to the responsible authority, these authorities having the power to curtail its use if the resistance is pervasive. However, marketing consents for pesticides are given on the basis of their quality, safety and efficacy at a particular point in time, based usually on data from the most recent field trials. Once in the market, a pesticide can be sold and used within the terms of its marketing consent until its safety or efficacy are called into doubt to such an extent that the terms of the marketing consent are changed. By then it is too late. The current system amounts to a reactive rather than a precautionary approach to the problem of resistance. There are no known cases of resistance to a biopesticide fading away once it has been identified; on the contrary, the resistance always seems to grow, sometimes spreading around the globe in two or three growing seasons.

1.2 Regulation

The current US and EU regulatory, marketing and intellectual property rights structures not only make it impossible to maximise the full biological and therefore agricultural benefits of biopesticides. They actually guarantee the loss of these biopesticides as useful agricultural tools and thus increase the risks involved in food production.

Opinion is now masquerading as fact and vested economic interests frequently masquerade as science. We have decided therefore to separate so far as we can, the science and the politics from one another.

1.3 History of Science

Chapter 2 presents a chronological history of the scientific discoveries concerning Bt, including the emerging problem of insect resistance. We review the scientific evidence on resistance and the possibility of managing resistance. The consensus amongst entomologists is that all insects targeted by Bt crops will eventually become resistant and the current debate is about how best to delay its onset. Bt has been used by organic farmers as an external spray for over 50 years. Used as a spray, the toxin is effective for 3-5 days. When used in Bt plants the toxin is usually expressed throughout the plant for the whole of the growing season. Although entomologists agree that Bt plants are more likely to result in insect resistance than Bt sprays, key sections of the agrochemical industry, and Novartis in particular, continue to argue that Bt plants are safer than Bt sprays.

Insect resistance to Bt sprays was first reported in the field in 1979 and resistance to Bt plants has been developed in laboratory experiments. Insects bred under laboratory conditions can become several thousand times more resistant to Bt than those naturally occurring in the field. Although all sides of the argument appeal to scientific principles regarding the question of managing insect resistance, we have come to the conclusion that the argument can only be understood as a political conflict between commercial and environmental interests.

1.4 American Politics

Chapter 3. reviews the debates that have been held in the USA regarding the regulation of Bt crops over the past 10 years. There are now several million hectares of Bt maize, Bt cotton and Bt potatoes grown commercially in the US and a political (masquerading as scientific) consensus has been developing between entomologists, environmentalists and the agrochemical industry on how to delay resistance to Bt plants. According to this consensus, the best strategy, given that Bt crops are now being grown on a massive scale in repetitive monocultures (i.e. after any prospect of long term control has already been undermined), is to produce crops that are highly toxic to the target insects whilst at the same time providing 20-40% refuges of non-toxic plants to reduce the biological advantage of mutant insects resistant to Bt. It is, however, agreed that Bt now has a limited life as an effective toxin and this will result in organic farmers and integrated pest managers losing an extremely useful biopesticide.

1.5 European Politics

Chapter 4. reviews the European situation, where only Bt maize has been commercialised to date, mainly in Spain and Portugal but also in France and Germany. The European regulation of Bt crops is weak, incoherent, confused and inadequate by comparison with the policies adopted by the Environmental Protection Agency in Washington. One particular problem in Europe is that the use of Bt sprays is dealt with by one set of administrators working under the terms of the Pesticide Directive, whilst the use of Bt plants is dealt with by an entirely separate set of administrators working under the terms of the Directive on the Release of GMOs (Dir1990/220). The revisions to Dir 90/220 that have now been agreed might improve slightly the ways in which Bt crops are approved and managed in the EU but the revised directive is incapable of managing the sustainable use of biopesticides.

1.6 Future Scenarios

Meanwhile, the future use and management of Bt crops in Europe will be determined by three factors:

1. - the outcome of a complex mess of court cases between the European Commission, Member States, the agrochemical industry and non-governmental organisations.
2. - the refusal of the market (ordinary people, ordinary consumers), which is making it increasingly difficult if not impossible to sell Bt maize within the EU- and which then leads first to the food industry and then to the farmers refusing to use the Bt maize.

3. - direct action by groups of citizens who are simply outraged by the aggressive behaviour of Novartis and Monsanto and deem it their duty to destroy Bt crops in the field.

Chapter 5. concludes that the European Commission is considerably farther away from developing adequate policies for the sustainable use of plant biopesticides than the US Environmental Protection Agency. There are many questions that remain unanswered about Bt and until such time as the science is improved, any attempt at sustainable management will be based on best guesses. It is irresponsible to give marketing consents for Bt crops before adequate policies for their management are in place. If for any reason, be it biological, technical, political or economic, it proves impossible to devise a strategey for the sustainable use of Bt crops, there is only one responsible conclusion - they should quite simply be banned.

If future biopesticides are beset by the same combination of economic (market) and biological (resistance) mechanisms as Bt, the insect resistance problem will simply accelerate. For the moment almost all attention focuses on the search for biological or agricultural solutions to the problem. The notion that it might be the structure of the market that is the main cause of the problem scarcely receives a mention. The notion that it might be easier to sustain biopestides and plan secure food production systems by restructuring the economic rationale of the pesticide sector rather than by trying to constantly re-engineer biopesticides on the pesticide treadmill is what this report explores.

CHAPTER 2. THE SCIENCE

2.1 A Short History of Bt

Bt is a naturally occurring soil bacterium. Little is known about its natural life cycle, distribution or ecology, or its effects on other soil life. It was first detected in 1902 in the dying larvae of Bombyx mori by Ishiwata, who reported his finding in "Pathology of the Silkworm". It was first isolated from the larvae of Ephestia kuehniella by Berliner in 1913 after he noted that it had the capacity to kill certain insects in their grub stage (Z.Angew Entomologie 1915,2, p29).

2.1.1 Early Development

According to an article by Jacobs in the proceedings of the Society of Applied Bacteriology (1950,13 p83) Bt seems to have been used for the first time as a microbial biopesticide against lepidopterous larvae in 1938, thereby giving Bt a role in food production that it has had ever since. The extent to which Bt poisons insect grubs in natural ecosystems has never been studied and remains unknown. This means that it is impossible to predict the consequences of widespread insect resistance to Bt in natural ecosystems, should this occur as a result of its present commercialisation.

The Bt bacterium is easily propagated and can be used as a wettable powder or in a water solution. Bt became commercially available before the Second World War and was used mainly by vegetable growers to eliminate caterpillar infestations. The producers of Bt were typically small family firms operating to a large extent by mail order. Bt was simply one product in the wide armoury of naturally occurring insecticides that were commonly used before DDT ushered in the age of synthetic chemical insecticides during WWII. For the more sophisticated grower, Bt had an advantage over other natural insecticides such as nicotine or pyrethrum (for instance) in that it was fatal only to a small range of insects and left beneficials such as lacewings and ladybirds untouched. In the absence of research on the various Bt strains available, it can be assumed that the products sold on the market consisted of mixtures of strains in unknown proportions. This would have resulted in unexplained differences in the effectiveness of different Bt products, which would presumably have affected growers perceptions of its efficacy. Bt was thus an unreliable product during this period. Some growers (who perhaps by luck had got hold of the strain most effective for their purposes) swore by it; others (who perhaps had the bad luck of getting less appropriate strains or mixtures) regarded it as pretty much useless.

There is no evidence of large scale use of Bt for the first 50 years of its known existence, nor of any research on the various strains of Bt in existence. No one understood why it worked or how it worked, so no one could explain why it sometimes worked effectively, whilst at other times this was not the case. There were too many variables in the field and no one had tested Bt in the laboratory.

There was nothing intrinsically ecological or organic about the use of Bt up to WWII. Indeed, had Bt been more reliably effective, its commercial use might well have expanded to the point of causing resistant insects to dominate their populations. Luckily, Bt was used intermittently and sparingly so it survived as a useful insecticide. It is important to note that the survival of Bt as a useful insecticide was not due to superior knowledge or practice. Its survival was a good accident.

2.1.2. 1940-1960 The Uncritical Age for Synthetic Pesticides

Bt and most interest in it was eclipsed during the uncritical hey-day of synthetic insecticides, lasting from WWII through to the publication of "Silent Spring". For some 20 years, Bt was only of interest to those growers who - for one reason or another - did not want to use the new synthetic insecticides.

During this period, the arguments of those who refused to use the synthetic products were easily marginalised as "unscientific":

- they could give no scientific explanation why their methods worked or sometimes failed to work,
- the evidence we now have of the widespread harmful effects of many synthetic pesticides simply did not exist,
- the new synthetic products were reliable, effective and their mode of action understood
- ecological thought existed only at a philosophical level and had little in the way of a scientific base

After a generation of largely uncritical use, two difficult facts about the synthetic insecticides had to be acknowledged:

- they caused widespread biological destruction and environmental pollution way beyond their insect targets
- constant use caused resistant insects to dominate the target populations, rendering the products useless

The search was on for alternatives.

2.1.3. 1960-1990 Bt becomes Big Business

There are four basic reasons why the agrochemical industry became interested in Bt.

1. The cost of developing new chemical pesticides was soaring to between \$35-\$40 million whereas the cost of developing a biopesticide was less than \$5 million (Bioprocessing Technology, June 1988).
2. The timescale for developing a new chemical pesticide is 8-12 years whereas biopestides can be brought to market in about three years (Bioprocessing Technology, June 1988).
3. Given the acceleration of insect resistance to chemical pesticides, and the time it was taking to bring new ones to market, analysts predicted the possibility of a gap opening, in which some crops would be left with no viable means of chemical defence against insect pests.
4. Scientists are dreamers too. For reasons that no one is now able to explain, it was once widely believed by entomologists that Bt was not only an environmentally friendly biopesticide, but also one which insects could not get around. They were sure that insect resistance would never be a problem.

Bt was described as "the wonder pesticide" and the panacea for all the ills of the pesticide industry even though many insect pests were, and probably always had been naturally resistant to Bt.

A few chemical majors started moving into Bt -

Abbot Laboratories (USA)
American Cyanamid (USA)
BASF (Germany)
Caffaro (USA)
Crop Genetics International Corp (USA)
Ecogen (USA)
DeKalb (USA)
ICI - now Zeneca (UK)
Mycogen (USA)
NovoNordisk (Denmark and USA)
Rohm & Haas (USA)
Sandoz (Switzerland and USA)

Laboratory research on Bt strains and targets started in the 1960s and the market for Bt grew fast in forestry and in vegetable production. Current patterns and volumes of conventional Bt use on some vegetables and fruits in the USA are already high and almost certainly unsustainable. There are four main sub-species of Bt:

Bt aizawai
developed by Sandoz (Novartis)
used against lepidopterous larvae,
produced by Sandoz ("Certan"), NovoNordisk ("Florbac") and Abbott ("Xen Tari")
Bt israelensis
developed by Sandoz (Novartis)
used against mosquito and blackfly larvae
produced by NovoNordisk ("Bactimos") ("Skeetal"), Caffaro ("Bactis"),
Abbott ("Gnatrol") ("Vectobac"), Sandoz ("Teknar")
Bt kurstaki
developed by Ecogen and Sandoz
used against lepidoptera larvae in agriculture, horticulture, forestry, also Colorado Beetle

produced by NovoNordisk, Novartis, Ecogen, Abbott, Roussel-Uclaf, Intrachem under 19 different trade names,
Bt tenebrionis
developed by NovoNordisk
used against Colorado Beetle
produced by NovoNordisk ("Novodor")

The statistics on the application of microbial Bt are not complete. In the USA 57 crops were being treated with Bt on 2,037,834 acres by 1992. Six crops were largely dependent on Bt, with over 80% of planted areas being sprayed in some states. See the tables in Annex 4 for more details.

2.1.4. 1980 - 2001? Bt crops

"The scientists studying Bacillus thuringiensis and the companies spending millions of dollars bringing it to market say they are absolutely sure about one thing: Bt, as it is known - a species of microscopic bacterium found in almost every handful of soil the world over - has the potential to replace an entire generation of chemical pesticides.....Even in the past two or three years, as Bt has achieved almost celebrity status amongst those who make a living thinking of better ways to kill bugs, and as scientists have embarked on a world-wide hunt for new strains of the microbe, the questions surrounding Bt have only grown......How on earth, some scientists would like to know, did this seemingly innocuous soil bacterium develop such a powerful and selective weapon against insects? There are theories, of course. But they are all so speculative and sometimes so contradictory that it seems likely Bt will make millions for its manufacturers long before it is fully understood by scientists." (Washington Post 27.11.89)

Some of the companies already investing in Bt sprays moved into genetically engineered Bt plants but on the whole, the Bt market has split into two more or less exclusive groups. The genetic engineering companies with interests in Bt plants include the following:

Agracetus (USA)
Agricultural Genetics Co Ltd (UK)
Agrigenetics Advanced Sciences Co (USA subsidiary of Lubrizon)
Ciba-Geigy (Switzerland, now Novartis)
DeKalb (USA)
Monsanto (USA)
Plant Genetic Systems (Belgium)
Sandoz (Switzerland, now Novartis)

By 1997 these companies were field testing at least 18 different Bt crops, including trees that could be expected to live for 150 years or more:
Alfalfa
Allegheny Service Berry
Apples
Aubergines
Broccoli
Cotton * in commercial production USA 1996
Cranberry
Grapes
Maize * in commercial production USA 1996, EU 1998
Peanuts

Poplars
Potatoes * in commercial production USA 1996
Rapeseed
Rice
Spruce
Tobacco
Tomatoes
Walnuts

2.1.5. Beyond Bt

It is generally agreed by entomologists that the biologically useful life of Bt is now limited. The question that most scientists are asking is not *whether* insects will become resistant to Bt, but *when* this will happen and whether there is anything that can be done to delay the process that is now inevitable. Convinced that biopestides will join chemical pesticides on the resistance treadmill, entomologists and the genetic engineering industry have already identified the next panacea as Photorhabdus luminescens (PhL for short). The mere fact that a consensus has developed around the potential use of PhL has self-fulfilling implications. In effect, the market destroys the product. It can be predicted with some certainty that PhL and PhL plants will also have a limited usefulness and that after PhL the industry will be searching for yet another panacea for the problems that they themselves create.

2.2 The Mode of Action of Bt Crystal Protein

Bt is a soil bacterium noted for its abundant production of insecticidal proteins in the form of a crystal or crystal-complex during sporulation. The insecticidal crystal proteins are called "cry" proteins and the genes encoding them as "cry" genes. Cry proteins have been classified according to the range of insects for which they are poisonous and for their nucleotide sequence. However, this does not result in the categorisation of cry genes into exclusive classes. For example, members of the same protein class can vary significantly in their poisonous effect against insects within a single insect order. Equally, the same protein isolated from different Bt strains can vary in its amino acid sequence, resulting in dramatic differences in their poisonous effects.

Table. Bt Cry Proteins and their Pest Targets

Gene	sub-type	Crystal Shape	Protein Size (kDa)	Pest Target
Cry1	A(a), A(b), A(c), B, C, D, E, F,G	Bipyramidal	130-138	Lepidopteran larvae
Cry2	A, B, C	Cuboid	71, 71, 69	Lepidopteran and Dipteran larvae
Cry3	A, B, B(b)	Flat or Irregular	73, 74, 74	Coleopteran larvae
Cry4	A, B, C, D	Bipyramidal or Round (?)	134, 128, 78, 72	Dipteran larvae
Cry5-CryIX		Various	129, 73, 35, 38	Various

(Hofte and Whiteley, 1989; Microbiol. Rev. 53:242).

More than fifty cry proteins have now been sequenced and the simplified classification shown above is no longer adequate. Classification schemes based solely on sequence data create a different picture of the relationships among the various Bt proteins, and perhaps more accurately reflect the evolutionary relationships between the various cry proteins.

The Cry proteins do not become biologically active toxins until they have been dissolved in liquid and activated. Normally this occurs in the highly alkaline mid-gut environment of lepidopteran insects. The toxin is activated by the insects gut enzymes. Most mammalian guts are acidic and do not produce a favourable environment for the Cry toxin. It is generally accepted that the toxin recognises certain receptors on the surface of insect mid-gut epithelial cells. A pore-complex forms through the cell membrane, resulting in the loss of potassium ions which affects the insect's ability to regulate osmotic pressure. Eventually the animal dies due to massive water uptake.

According to DeWald (1995), "crystallography studies with Cry IIIA protein toxin (Li, et al; 1991. Nature 353:815) indicate three structurally distinct domains. Domain I consists of seven alpha-helices and is believed to be involved with membrane interactions and the insertion of the toxin into the insect's mid-gut epithelium and pore formation. Domain II appears as a triangular column of three beta-sheets and is reported to be involved in receptor binding. Domain III consists of anti-parallel beta-strands in a "jellyroll" configuration and, like Domain II, is implicated in insect specificity and stability. It appears that several of the reported cases of insect resistance to specific Cry proteins are due to altered receptor binding specificities. Presently, our knowledge of the various Cry proteins is insufficient to predict how specific protein modifications may affect the efficacy or activity spectrum of a particular protein".

2.3 The Development of Bt Strains

Bt has been developed within two distinct paradigms - the "military" paradigm of the agrochemical industry and the "holistic" paradigm of the organic movement.

2.3.1 The Military Paradigm for the Development of Bt

Bt has been used as an active ingredient in a wide range of biological insecticides for nearly a half century. These products have been used in agriculture and forestry, and for the control of disease vectors such as mosquitoes and blackflies. In agriculture, many of the products have been based on a single strain of Bt, termed HD-1, that was isolated in 1970 at the USDA Cotton Insects Research Laboratory in Brownsville, Texas.

Since the early 1980's, research on Bt has shown that the Cry proteins produced by sporulating cells are encoded on extrachromosomal plasmids. These plasmids are capable of being transferred between strains of Bt by a conjugation-like process. It has also been shown that many strains of Bt have several Cry genes, thus producing either multiple insecticidal crystals or mixed crystals containing several different but related Cry proteins. Bioassays of individual purified Cry proteins have shown that each one has a unique range of target insects in the Lepidoptera (caterpillar), Coleoptera (beetle) or Diptera (fly) groups. Some thirty or more different Cry genes have been cloned and sequenced. By a process of cloning and expression of individual Cry proteins in a common Bt strain background, it is now possible to identify those that are particularly active on various target insects, and to use genetic techniques to construct strains carrying several Cry proteins selected for both optimised activity on the desired insect targets and for the management of the potential for insect resistance.

Bruce Carlton at Ecogen was full of optimism in 1995:
"We have utilised these approaches to construct a number of new Bt strains for different crop and insect applications. The choice of Bt itself as the expression host has several advantages. First is that Bt is naturally capable of stably maintaining several different ICP (Cry) genes without undergoing loss or gene rearrangement. Second, Bt can express these genes to high levels such that 25-30% of its total protein can be ICP (Cry) protein. Third, we can take advantage of natural Bt plasmids as cloning vectors for constructing new ICP (Cry) combinations, as well as a Bt transposon that encodes both a transposase and a site-specific recombinase. These elements greatly facilitate the construction of new ICP (Cry) combinations that do not contain antibiotic resistance genes or other undesired foreign genes. Thus, the new Bt constructs consist only of Bt DNA, a definite advantage when seeking regulatory approval for conducting large-scale field trials or product registration."
In fact, Ecogen was granted a blanket approval in 1992 by the Environmental Protection Agency for conducting small-scale field trials of any new recombinant Bt without having to obtain separate approvals by employing exactly this strategy.

According to Carlton, ‘Ecogen's first new product derived by this recombinant technology is called Raven, and was developed as a superior product for control of Colorado potato beetle, as well as caterpillar pests of potato, tomato, and eggplant. This product, the first live Bt derived by recombinant DNA technologies, was approved for registration by the EPA within ten and a half months of submission. The Raven strain contains two different ICP proteins of the beetle-active CryIII group, in addition to two caterpillar-active CryI genes. The two CryIII genes contribute to a much higher productivity in fermentation of this strain as compared to its predecessor strain in the now-discontinued Foil product."

Carlton argued that ‘the particular combination of genes in the Raven strain is designed to minimise the development of resistance to the product by the Colorado potato beetle, which is recognised as perhaps one of the most active of all insect pests in developing resistance to chemical insecticides. This strategy involves two different approaches.

First is that the two CryIII proteins expressed in the Raven strain have different binding characteristics on potato beetle midgut cell membranes. In studies conducted with researchers at Michigan State University, laboratory-selected potato beetles that are resistant to one of the CryIII proteins showed only minimal resistance to the second CryIII. Thus, in practice, an individual beetle would have to undergo two independent resistance mutations to become resistant to the Raven product.

Second, it was found that when the beetle strain selected for resistance to the one CryIII protein is exposed to a mixture of that CryIII protein and the CryI protein contained in Raven, the CryIII resistance is strongly reduced. This effect is presumably due to some protein-protein interaction that occurs between the two ICPs at the level of midgut binding. Thus, the Raven strain incorporates two different strategies to minimise the likelihood that the principal insect target would develop resistance to the product.

Currently there are two other products under development using the recombinant system described, one (CryMax) for applications on an array of caterpillar pests of vegetables and horticultural crops, and a second (CryStar) specifically aimed at the control of fall armyworm on sweet corn and other vegetables, an insect for which no Bt product is currently available. In the future we expect to continue to develop novel ICPs that have different properties with respect to their modes of action on important insect pests. These activities will come from a combination of new gene discovery efforts and by employing approaches such as protein engineering of selected genes to alter their activities and other physiological properties. We believe that this combined approach will allow us not only to develop new and improved products, but also to effectively manage the potential for insect resistance development by continuing to exploit the ability of Bt to express multiple ICP genes having a diversity of activities."

2.3.2 The Holistic Paradigm for the Development of Bt

According to Kirschenmann, President of Farm Verified Organic Inc, "Organic farmers have traditionally avoided the use of synthetic materials in crop production because, as a rule, they short circuit, rather than enhance, the ecological balances of nature. Synthetic materials, consequently, often create the problems they purport to solve. For example, R. Hindmarsh has pointed out that annual crop losses to insects doubled during the same period of time that insecticide use increased tenfold (The Ecologist, Sept. 1991, pp.198-199)."

Bt sprays have been used successfully in diversified cropping systems as a limited-use pesticide for two generations. Traditionally the first organic line of defence against pests is to maximise the biodiversity of the farm and tghus minimise the vectors available for pests to spread. Applications such as Bt sprays are only used in emergencies and the likelihood of insect resistance emerging under such usage is minimal.

"If Bt is used persistently, pests are likely to build up resistance within a few years. The rule that appears to apply is that the more we homogenise production in the form of genetically uniform monocultures, the greater the risk of pests devastating the crop. And the greater the risk, the more we apply poisons, which in turn results in the insect population becoming resistant."

"Most farmers operate under very intense financial constraints. They are forced to make field management decisions based on immediate financial constraints and even though they may know that this can or will result in longer term problems for which there are no solutions, they are not economically free to behave otherwise. They are too preoccupied with today's headache to worry much about tomorrow's doom."

According to Kirschenmann (1995), "farmers in North Dakota were warned by everyone from extension agents to seed sales people, that failing to rotate sunflowers would invite sunflower insect and disease disasters. But sunflowers were a good cash crop that produced much needed revenue, so most farmers raised sunflowers in the same fields at least every other year, and in some instances they continuous-cropped them. Within a few years insect and disease problems became so severe that the cost of pest control forced many farmers to get out of sunflower production. It is not that farmers were stupid or unconvinced of the risks. Short term economics simply took precedence over long term economics."

In a holistic ecological system of complex interactions and reactions it is never possible to predict all the effects of the introduction of a novel organism. According to Kirschenmann, "examples abound. Just recently (New York Times, October 9, 1995) two USDA scientists reported that the infestation of the beet armyworm on Rio Grande Valley and San Angelo, Texas cotton crops may have been caused by heavy applications of malathion designed to eradicate the boll weevil. The malathion, they said, caused "a disruption of the beneficial insect complex that normally suppresses the beet armyworm." Transgenic crops, which introduce instantaneously-created new life forms into the environment, dramatically increase the potential for such disruptions, many of which may be irreversible."

An Example: integrated management of the Colorado Beetle
The September 1992 issue of 'The IPM Practitioner' is devoted entirely to IPM options for controlling the Colorado Potato Beetle. The key to the IPM approach is understanding the biology of the beetle.
The CPB overwinters between 6 and 20 cms beneath the soil in potato fields or in nearby border areas and woodlands. The adults ususally emerge just when the first potatoes are sprouting. They are unable to fly any distance at first and only regenerate their flight muscles if they do not find potato plants within five days. Virtually all overwintered beetles that colonise a non-rotated field originate from that field.

Different control methods are appropriate to each of the four stages in the life cycle of the beetle:

Table IPM Management of Colorado Potato Beetle

Season	**Stage in Life Cycle**	**Method**
winter	hibernating adults	crop rotation, tillage
spring	emergence of overwintering adults	trap crop, flame mulch & remove, barrier (wheat)
late spring	adults and first eggs	vacuum, flame, mulch nursery for predators: Coleomegilla maculata Chrysoperia rufilabris Edovum puttleri neem antifeedant
early summer	1st generation young larvae	mass release of predators, mulch
	1st generation larvae	Bt spray, cryolite, cyromazine
summer	1st generation pupae	Beauveria bassiana (fungus), nematodes
	1st generation adults	spiders (mulch), vacuum
late summer	egg laying adults	neem, release predators
	migrating adults	Bt, vacuum, Beauveria bassiana
autumn	overwintering adults	trap crop, flame

A rotation of maize or wheat with potatoes encourages ladybirds (Coleomegilla maculata) which eat CPB eggs. Maize and wheat also offer a barrier to CPB migration. In one experiment, only a little over 50% of CPBs released into a wheat field reached potato plants just three metres away. The ladybirds which overwinter in wheat fields ate over 50% of the CBM eggs, reducing CBM colonisation of the potato plants by 75%. The surviving CPBs can be concentrated on a trap crop of early potatoes, making physical control easier. Equally, late planting increases the mortality rate of CBM significantly.

According to Jeff Waage, Director of the International Institute of Biological Control at Imperial College, London, Bt could have had a good future if used within a system of integrated pest management.

"As a product, Bt is valuable in IPM systems because it is much less harmful to predators and parasites than broad spectrum chemical pesticides. Therefore it can be substituted for chemical products in "insecticide treadmill" situations and will allow the recovery of natural enemy populations. Like many biopesticides, it is often less effective on its own than a highly potent chemical product. However, in an IPM system, where it is used only when needed and it conserves natural enemies its impact is augmented by the action of those natural enemies and can be both more economical and sustainable.

However, present product registration and evaluation systems often neglect this, favouring through various procedures and protocols the development of "this is all you need" products.

A second problem facing Bt is the risk of resistance. Where Bt is used as a single technology solution, like its chemical predecessors, it is sprayed regularly and a range of insect pests are now developing resistance.

Bts third problem is that it lacks the most desirable property of a biological control agent: its ability to reproduce and perpetuate itself in crops. A key advantage of biological agents relative to chemical pesticides is their capacity to both kill pests (functional response) and reproduce at the expense of the pest (numerical response) thereby giving some control in future pest generations. Bt is not adapted to persist in the crop environment and its commercial development has focussed less on preserving its ability to reproduce and spread, but more on maximising the efffect of its insect-killing toxin. In other words, iits commercial development has focused on using it like a chemical pesticide and not as a living biological control agent. This is true of most biopesticide development today..... It also reflects the fact that the multinational agrochemical industries which have dominated biopesticide development have traditional skills which are limited to the production and marketing of pesticide-like products."

According to Waage, "Engineering genes for Bt toxins into plants is an ingenious method of delivering these toxins to pests which might naturally avoid them, such as insects which feed inside plants. From an IPM perspective, this technology has more similarities to plant resistance breeding than biopesticide development.... Biotechnology for plant protection is still in its early days. So far, it has been focussed conservatively on improving conventional pest control approaches, biological pesticides and vertical resistance in crops to pests, in order to make better, single-technology solutions to insect pest problems which will outcompete current, non-engineered products. IPM promotes a more diversified approach which will limit over-reliance on any specific technology and the consequences of this, such as resistance development. It promotes greater reliance on exploiting living, self-renewing processes in pest control, such as the action of natural enemies of pests." (Waage.J in Biotechnology & Development Monitor No 32 pp 19-21 1997).

2.4 The Development of Resistance to Bt

At least four species of insect have evolved resistance to Bt in the field and over ten species have evolved resistance under laboratory conditions. The latter figure is more a reflection of the number of experiments that have been carried out than the number of insects that could develop resistance. By presenting the crucial scientific findings in chronological order we show how the scientific research on Bt has generated a roller-coaster of undulating optimism and pessimism in the genetic engineering industry. With hindsight, it is easy to see that more account was taken of the optimistic findings than the pessimistic ones.

The resistance problem started in 1979 when **R. Kinsinger** published his paper on **"Susceptibility of populations of Indian Meal Moth and Almond Moth to Bt"** in the Journal of Economic Entomology Vol 72 pp 346-349. His laboratory studies showed a 42 fold increase in resistance to Bt. However, this study was largely forgotten and is infrequently cited. Moreover, when cited, the two moths have been treated as special cases since they live in bins of harvested crops which tend to be more heavily dosed with insecticides than insects in the field.

Two years later, **D. Briese** cast doubt on Kinsinger's findings in his chapter entitled **"Resistance of insect species to microbial pathogens"** in Davidson.E (ed) Pathogenesis of Invertebrate Microbial Diseases, Allenheld, NJ 1981
Briese summarised all the failed attempts to breed Bt resistant insects in the laboratory. This study led to the belief that insects in the field (as opposed to insects in bins) could not or would not become resistant to Bt.

However, four years later **W. McGaughey** published his paper on **"Insect resistance to the biological pesticide Bt"** in Science 229 pp193-195 1985. He reported on his laboratory selection showing a 27 fold increase in Indian meal moth and almond moth resistance after 2 generations, and a 97 fold increase after 15 generations. The study confirmed the Kinsinger findings but added nothing new to the debate other than to confirm that continued exposure to Bt led to increased insect resistance.

A year later, **A.Chang** published **'Defense Reaction of Mid-Gut Epithelial Cells in the Rice Moth Larva Infected with Bt"** in the Journal of Invertebrate Pathology 47 pp333-339 1986. This research identified the mid-gut reaction as the method by which the larvae defended itself from the Bt toxin. The study provoked the hypothesis that the development of Bt resistance was a specific reaction that could possibly be circumvented.

The statistical basis for generalising from laboratory experiments to the field was then questioned by **R. Roush** in **"Ecological Genetics of Insecticide and Acaracide Resistance"** which was published in the Annual Review of Entomology No 32 pp 361-380 1987 Roush analysed the laboratory results on resistance and concluded that laboratory insect populations are normally derived from small samples of the total gene pool of the insect and these normally develop polygenic resistance mechanisms which will not necessarily occur in the field. This study encouraged the belief that resistance in the field could not be predicted by cases of resistance developed in the laboratory. The importance of laboratory evidence was thus played down.

The enormous natural diversity of Bt strains was revealed by **J. Morrison** in **"Soil Yields 72 New Varieties of a Natural Pest Control"** published in Agricultural Research Vol 14 1988. Morrison reported the results of a world-wide trawl for Bt varieties which increased the number known from 24 to 96. It was found that the Mediterranean region had the greatest density of Bt in the soil. Bt was found at such high altitudes in Tibet that no known host organisms managed to exist there. Seventy two new Bt varieties were identified, some of them 20 times more toxic than existing commercial varieties. The findings led to the optimistic assertion that naturally occurring Bt strains could provide the basis of a comprehensive insecticide resource for the foreseeable future.

There was further cause for optimism when **G.Georghiu** published his famous book on **"The Occurrence of Resistance to Pesticides" FAO Rome 1988** Although the book is mostly a documentation of innsect resistance to insecticidces it also includes a summary of unsuccessful attempts to produce Bt resistant insects in the laboratory. This led to renewed hopes that the resistance of the Indian meal moth and almond moth to Bt were exceptions rather than the demonstrations of a rule.

As the commercialisation of conventional Bt got underway, **David Ferro** argued that Bt sprays were compatible with systems for integrated pest management in **"Toxicity of a new strain of Bt to Colorado Potato Beetle** in the Journal of Economic Entomology Vol 82 No 3 1989. He argued that Bt san diego was compatible with IPM systems because it killed the Colorado beetle but left its predator ladybirds unharmed. The results of this study have been thrown into doubt by more recent research indicating the opposite phenomenon.

The same year **Ferro** argued for caution within the industry. The industry magazine **AGROW** (No 85 21/4/1989) began to question whether Bt was really unassailable in **" Bt - potential for pest resistance?"** The report of an Agbiotech Meeting held in Virginia hadDr Ferro noting "that any attempts to increase the effectiveness of Bt products will also increase the competitive pressure for resistance to develop. He therefore urged companies not to go too far in improving their Bt products." Whilst Ferro put his finger on the central contradiction, his recommendation was rather like asking sprinters not to run too fast in the Olympic Games.

Doubts about Bt increased when **T.Stone** published the **"Selection of tobacco budworm to a genetically engineered P. fluorescens containing the delta-endotoxin Btk"** in the Journal of Invertebrate Pathology No 53 pp 228-234 1989. This was the first report of laboratory selection of insects resistant to Bt as opposed to the reports of increasing resistance amongst insects that were already resistant. After 3 generations there was a three-fold increase in resistance and after 14 generations this had increased to 24-fold. This study severely dampened the optimism that had been generated by the Briese (1981) and Georghiu (1988) studies but it did not answer the argument made by Roush (1987) that laboratory studies were not necessarily a good predictor of behaviour in the field.

Later the same year **Stone** sent the Bt industry into a spin with a presentation of laboratory evidence on **"Insect resistance to Bt delta-endotoxins"** at the International Symposium of Molecular Insect Science, 22-27/10/1989, inTucson, Arizona. This was the first report of cross-resistance. Helicoptera virescens resistant to the Cry1Ab protein showed varying levels of resistance to Bt aizawai, Bt colmeri, Bt darmstadiensis, Bt entomocidus, Bt kurstaki and Bt thuringiensis. The study shocked entomologists and genetic engineers. The results could not be explained by existing models and they marked the end of the optimistic scenario in which an infinite variety of Bt subspecies could be used to constantly replace those Bt subspecies to which insects had become resistant. The industry set up a working group on Bt resistance in response to this study.

J. Van Rie was amongst the first entomologists to start searching for viable resistance management strategeies. In "**Mechanism of Insect Resistance to the Microbial Insecticide Bt"** published in Science Vol 24 on 5/1/1990 he argued that: "Strategies for resistance management are needed to extend the lifetime of chemical insecticides. It is equally important to implement such strategies with Bt to maintain its usefulness as a safe and environmentally sound insect control agent." Van Rie argued for the ‘pyramid’ approach to genetically engineered Bt plants. This entails the insertion of several Bt Cry proteins at the same time so that if one does not work the other one does. The initial laboratory results were sufficiently encouraging to justify the announcement of a whole new strategy against insect resistance. The argument for "pyramiding" toxic genes is still propagated by industry representatives in various parts of the world despite the fact that subsequence evidence on the development of cross-resistance and multiple resistance sharply reduces the number of combinations of Cry proteins that can be used simultaneously. The strategy has been rendered worthless by several factors which are considered in more detail below:

- many Cry proteins are only poisonous to specific insect species
- almost all crops have more than one economically important insect pest
- the same insect pest can eat several different crops in the same region
- insects can develop multiple resistance to several Cry proteins

From 1990 onwards the scientific literature contains any number of papers reporting the increase in insect resistance to Bt over several generations under laboratory conditions. The study by **D**. **Miller** on the "**Development of a strain of Colorado Potato Beetle resistant to the delta-endotoxin of Bt"** in the WRCC Newsletter No 2 p 25 1990 is an average example of a study showing showing a 67-fold increase in resistance after 10 generations. Studies of insect resistance to Bt had become standard material for an American Phd in entomology.

The first of several bombshells from the American entomologist **Bruce Tabashnik** was published as **"Field Development of resistance to Bt in diamondback** moth"in the Journal of Economic Entomology 83 pp1671-1676 1990. Diamondback moths were found to be largely resistant to watercress sprayed with Btk in Hawaii. According to Tabashnik: "The lack of previous reports of substantial field resistance to Bt led many to conclude that such resistance was unlikely, particularly in defoliating crop pests........Expression of Bt toxin genes in crop plants and other related advances in technology are likely to intensify selection for resistance to Bt." This was the first study proving that Bt resistance could develop in the field since the 1979 study by Kinsinger. It finally resulted in entomologists and genetic engineers realising that insects would develop resistance to Bt just as they did to chemical insecticides.

After the Tabashnik study put resistance firmly on the map, laboratory experiments were designed to elucidate the dimensions of this resistance. In 1991 S.Sims reported on the **"Genetic basis of tobacco budworm resistance to an engineered Photorhabdus fluorescens expressing Btk"** in the Journal of Invertebrate Pathology No 57 pp. 206-210 1991. He showed that tobacco budworm with an initial Bt resistance 69 fold greater than normal fell to 13 fold greater after 5 generations of non-exposure to Bt. These findings by Sims indicated that occasional use of Bt, or the use of Bt within a rotation of different insecticides, might overcome the resistance problem, since insects showed much reduced resistance after a few generations. However, instead of leading researchers into making some potentially fruitful IPM/ICM field studies, the Sims study led mainly to a host of laboratory experiments designed simply to indicate whether insect resistance would continue to reduce back to zero with subsequent generations, thus giving some hope for its sustainable use. (It is worth noting in passing that PhL was at this time being used as a host to Bt rather than as an insecticide in its own right.)

Still working on conventional uses of Bt, **David Ferro** reported on a study of the conditions under which sprays are most effective in **"Colorado Potato Beetle Larval**

Mortality: operative effect of Bt san diego"published in the Journal of Economic Entomology Vol 84 No 3, 1991. His study showed that timing and temperature were crucial. Larvae could not survive more than 6-8 hours of Bt.sd. when the temperature exceeded 24 centigrade, indicating however, that this Bt might be ineffective in the northern range of the beetle. There are many studies of the conditions under which Bt sprays are most effective and they mostly point up very specific conditions which are difficult to replicate in the field. These problems have in turn been used to justify the production of Bt plants on the grounds that they are more effective and require less skill from the farmer. Bt plants are of course more effective for killing borer insects, most of which are well protected from Bt sprays by the fact that they live inside the plant.

In 1991 **J. Ferre** drew further attention to the problem of cross-resistance to Bt in **"Resistance to the Bt bioinsecticide in a field population of P. xylostella"** published in Proceedings of the National Academy of Sciences Vol 88 pp 5119-5123 1991. He showed that Diamondback moths resistant to Cry1Ab toxins were also susceptible to Cry1B and Cry1C toxins. The previous study of cross-resistance by Stone in 1989 dealt with Bt sub-species which each produce either a number of different Cry toxins, and/or the same Cry toxins in different proportions. Ferre pinned down the multiple resistance to particular Cry toxins, which made it possible to speculate as to whether Bt genes could be designed to contain particular Cry toxins and whether these could then be specifically combined as pyramids of multiple toxins, or used in planned rotations of different toxins from one year to the next.

By 1992 a clear schism was developing between entomologists and the industry. Whilst the industry continued to carry out field trials one Bt crop after another, the entomologists were increasingly sounding a note of alarm. Perhaps with some justification, the industry tended to treat these interventions as a way of fund-raising pet research projects. M. Caprio published an article on **"Arresting Resistance"**in Bio/technology Vol 10 May 1992 in which he said that "it will be important to evaluate genetic variation for resistance, and the potential magnitude of resistance in target and non-target pests exposed to Bt, as well as the patterns of cross-resistance among Bt toxins. Until these data are available, it is prudent to treat susceptibility to Bt as a limited resource, and concerted efforts should be made to delay the evolution of resistance." However, Caprio's plea for the time to get the science right and plan strategies to deal with insect resistance to Bt was not compatible with the rush to get Bt products into a highly competitive market where the winner was likely to get all.

The work reported by Chang in 1986 indicated that resistance to Bt was associated with changes in the mid-gut. Other work had indicated that resistance to Bt was still limited to specific strains and it was thought that resistance was inherited as a partially or fully recessive trait. This had led to optimistic plans for the management of resistance. However, work reported by **Fred Gould** in **"Broad spectrum resistance to Bt toxins in Heliothis virescens (Bollworm)"** in Proceedings of the National Academy of Science Vol 89 pp7986-7990 September 1992 called all of this into doubt. Gould showed that a laboratory strain of the bollworm developed cross-resistance in response to a Cry1A(c) protein, including resistance to very different forms of Bt. The resistance was not associated with any changes in the mid-gut and the trait was inherited as an additive trait when larvae are treated with large doses of Cry1A(c) protein. The study confirmed the general scientific ignorance of the resistance mechanisms at work, and called into doubt the possibility of planning precise strategies for delaying insect resistance, just at a time when other scientists were beginning to declare the possibility of understanding and planning for cross-resistance.

The situation became further confused with **David Ferro's** mathematical modelling of the development of resistance in dynamic insect populations. He reported on the **"Potential for Resistance to Bt in the Colorado Potato Beetle"** in the American Entomologist Vol 39 No 1 1993. This study concluded that plants expressing LOW levels of Bt toxin which slowed the rate of larval development might produce the best long-term control of the Colorado Beetle. The study thus undermined the growing scientist-Monsanto consensus that highly toxic Bt plants grown with an insect refuge would provide the best possible insect control, plus the best possible management of insect resistance. It was, however, music to the ears of Novartis, which happened to be stuck with a Bt maize expressing low levels of toxin during the latter part of the season which did not fit well with the high toxin/refuge strategy for managing resistance.

Fred Gould shifted ground and was one of the first entomologists to argue that although the high toxin/refuge strategy might not be the panacea it was once thought to be, it nevertheless offered the best trade-off between ecological and economic interests and was thus the most likely strategy that the genetic engineering industry would accept. The entomologists were by now trying to find an accommodation with the economic interests of the industry. In **"Insect Resistance to Bt Toxins - can it be delayed?"** published in the Proceedings of the 2nd Canberra Bt Meeting 1993, Gould reviewed evidence for various strategies, concluding that the high dose/high refuge strategy was the most realistic strategy to follow. "Executing this strategy properly in local areas will require local research on pest/natural enemy population dynamics as well as education of local crop managers so that they can make informed decisions........Only solid local ecological research will allow us to determine how to put the least selective pressure on the pest while lowering its numbers and damage to acceptable levels." This paper marked the entry of the entomologists into the economic world of the genetic engineering industry. Science now became mixed with "economic realism", resulting in the political concept of "a trade-off between economic and ecological interests". Gould the entomologist began here to look at the problem from a commercial point of view. At the same time he argued, with justification, that the only way of managing insect resistance was by devising local strategies based on local ecological research, something which he knew was prohibitively expensive and could never be financed by the genetic engineering industry.

Gould's demand for local management resistance strategies was thoroughly supported by the study reported by **T.Stone** on the **"Geographic Susceptibility of H. virescens and H. zea to Bt"** published in the Journal of Economic Entomology Vol 86 No 4 1993. Insects collected from 12 states in the USA showed significant differences in susceptibility to Bt. If Gould's views on the need for local research on local conditions needed empirical justification, Stone provided it in plenty, thus questioning the desirability and efficacy of using the same Bt spray or Bt plant even against a single insect species. The same Bt product could end up working as a LOW level toxin in one place and as a HIGH dose toxin somewhere else, depending on the susceptibility of the insects.

Graham Head is one of the many entomologists who have moved between academia and industry. In 1998 he was working for Monsanto but the research he reported in 1994 was not particularly convenient for the company. In the **"Quantitative Genetics of Behavioural and Physiological Resistance to Insecticides in Diamondback Moth and the Colorado Potato Beetle"**published in Resistant Pest Management Vol 6 No 1 1994 he showed that the Colorado Beetles which are most responsive to Bt and non-Bt plants are also the ones that are most resistant to Bt. "Larvae moving onto transgenic foliage in a mixture are more likely to return to the non-transgenic foliage and survive if they are more resistant, making the seed mixture strategy potentially counter-productive." Head provided an argument against using seed mixtures containing Bt and non-Bt plants, and against Bt plants that did not uniformly express Bt. His findings were damaging to the random refuge strategy if the larvae moved between the refuge and the Bt crop, but the refuge strategy should still work if it were only the adult beetles that moved between the refuge and the Bt crop. The implication was that the spatial design and juxtaposition of refuges and Bt crops would thus determine the effectiveness of a refuge strategy. almost all refuge strategies from this time on advocated block planting of Bt and non-Bt crops alongside one another rather than mixing them in the same rows.

Mark Whalon introduced a further complication in **"Bt Resistant Colorado Potato Beetle and Transgenic Plants"** published in Biocontrol Science and Technology Vol 4 pp 555-561 1994. He argued that "given the use of Bt products as conventional insecticides has increased sharply, it is likely that a degree of selection by Bt may have occurred in field populations by the time the transgenic plants are introduced...... Several models suggest that providing alternative hosts (seed mixtures or refugia) can significantly slow the development of resistance, resulting in a portion of the population that is not selected, which supplies susceptible genes to the next generation. However, if the Colorado potato beetles do not have the genetic capacity to survive high Bt expression levels in transgenic plants, seed mixtures may be counter-productive." The reality is probably more complicated than Whalons theoretical model. If Bt potatoes are planted where there are already populations of beetles resistant to certain Bt sprays containing particular Cry toxins, the best strategy would be to plant Bt potatoes containing different Cry toxins which have not (yet) succumbed to multiple resistance. If this were not possible, the next best strategy would be to plant potatoes expressing high levels of toxin in the hope that the already resistant beetles could niot survive such an onslaught of poison. However, if this strategy failed, the Bt potato would become ineffective in just a few weeks.

Whalon eventually concluded that there were no answers to his questions. In **"Insect Resistance to Bt"** he wrote that "the development of genetically engineered plant with Bt toxins is not without controversy in our society, but it now appears that transgenic plants containing Bt will be approved in the same manner as genetically altered conventional Bt products. How conventional and genetically engineered plants with Bt toxins will exert selection pressure on pest populations individually and together is not understood." The dilemma outlined in commenting on Whalons first paper above is the subject of this contribution, which concludes that there is no scientific basis for predicting the outcome where both Bt crops and Bt sprays are used.

Richard Roush experimented with Whalon’s dilemma and reported his findings in**"Managing Pests and their Resistance to Bt - can transgenic crops be better than sprays?"** published in Biocontrol Science and Technology 1994. He showed that a strain of Colorado Beetle could survive Bt sprays but could not survive on Bt potato plants, even those expressing very small quantities of Bt. He argued that "this suggests that more mechanisms are available for resistance to sprays than to transgenic plants." Although the problem that Whalon grappled with was partly answered by Roush, the implications of his experiment depend on the reasons for the findings. Unfortunately there is no single explanation. The paper does not tell us whether the Bt spray and the Bt potato used in the experiment both contained the same Cry toxin(s) in the same proportions. If the answer is yes then the results are interesting, but if the answer is no, the results are neither interesting nor surprising.

Bruce Tabashnik produced a seminal review of the state of the art, or rather, the state of ignorance in "**Evolution of Resistance to Bt"**published in the Annual Review of Entomology Vol 39 pp 47-79 1994. "Results from laboratory selection experiments show that evolution of resistance to Bt is possible in moths, beetles, mosquitoes and other flies. Pests can develop resistance to a variety of Bt strains and toxins, even when many toxins are used simultaneously.......Knowledge of how different management tactics affect rates of resistance development is sorely needed........Until the tactics of managing resistance to Bt are rigorously evaluated, we must admit and accept the consequences of our ignorance. Theoretically one could use Bt extensively, perhaps in combinations or high doses, and somehow avoid resistance, but virtually no experimental evidence supports these approaches. Because intensive use of Bt could potentially produce rapid and widespread resistance, the burden of proof rests heavily on those who advocate attempts to overwhelm pests with Bt......Although genetic variation for resistance may be somewhat less for Bt than for conventional insecticides, the limited use and low persistence of Bt are probably the primary reasons for the scarcity of resistance to Bt in the field so far. The surest way to conserve the efficacy of Bt is to use it judiciously in conjunction with other controls." Tabashnik warned against what has now happened.

Faced with the growing list of insoluble problems associated with resistance management strategies, **T. Watson** came up with a straightforward military plan for the eradication of the pink bollworm on cotton. In a letter to R. Lavis dated 20/9/95 he proposed the following:
"As I see it this (Bt) technology can be utilised in either of two ways: management of pink bollworm or eradication. The former would be more applicable to an individual grower or community effort while the latter will need a total industry commitment.... Based upon my experience in all aspects of pink bollworm research I'll offer the following thoughts for consideration by the ACGA group who will be considering the eradication option.

1. It will require a two year commitment.
2. Cultural control must still form the basis for the eradication program.
3. All acreage must be planted with Bt-transgenic cotton
4. A planting window (by zones) and a mandatory termination date (by zones) should be strictly adhered to. This would reduce the likelihood of pink bollworm surviving in late season bolls when the expression would accelerate the development of resistant populations.
5. Utilise a good pink bollworm pheromone monitoring program.
6. Continue using your PCA's to manage all pests and monitor for pink bollworm.
7. There should be no need for conventional insecticides against the pink bollworm and some other lepidoptera pests......

There is indecision and controversy about how to deploy Bt-transgenic cotton to prevent the development of resistance. The present strategies being proposed are in variance with the plan I have proposed above. Most plans include a refugia whereby some pink bollworm will survive in non-Bt cotton. This is a logical plan for resistance management but incompatible with an eradication effort."

The eradication option was eventually rejected as unworkable. There was the danger that if 100% of US cotton acreage was planted with Bt plants, the pink bollworm would survive in the form of a 100% resistant insect. Either way, the result would not have been commercially advantageous to Monsanto, the sole developer of Bt cotton.

In 1995 Tabashnik threw further doubt on the usefulness of simple models of insect resistance and emphasised how little was really known about resistance to Bt. In **"Diamondback Moth resistance to Bt"** (email edition 1995) he wrote that "many field populations of diamondback moth (DBM), Plutella xylostella, have evolved resistance to Bacillus thuringiensis kurstaki (Btk) (Tabashnik 1994). Resistance to Btk in DBM did not cause cross-resistance to Cry1C, a major toxin in Bacillus thuringiensis aizawai (Bta). In laboratory selection studies, several insects have evolved resistance to Cry1C. Although low-level resistance to Bta was found in some field populations of DBM 1995, no previous cases of resistance to Cry1C have been reported from the field. Recently, we found that a Btk -resistant DBM field population in Hawaii evolved 20-fold resistance to Cry1C toxin less than two years after Bta products were used .... Our results suggest that Btk-resistant DBM populations can evolve resistance to Cry1C in the field in less than two years. In the NO population, resistance to Cry1C apparently evolved faster than to Bta. Several factors might cause the difference: (1) spores in Bta (2) toxins in Bta other than Cry1C, (3) Bta materials other than spores and toxins, or (4) formulation ingredients. The difference in resistance of DBM between Cry1C toxin and a Bta spore-crystal formulation suggests that spore-crystal formulations may be more durable than single toxins. Our data, however, do not address the more difficult issue of whether it is best to combine toxins or to deploy them sequentially."

In previous reports the DBM resistance to Bt was unstable and the insect again became susceptible to Bt after about 10 generations. However, in **"Stable resistance to Bt in Plutella xylostella (DBM)"** published in Resistant Pest Management Vol 7 No 1 1995 **Richard Roush** reported a stable, high level of resistance to Btk even in the absence of further selection. According to Roush, "this presents tremendous problems for developing resistance management strategies." These results confounded a lot of previous studies, though it is possible that there were crucial differences in the patterns and persistence of resistance to Bt between different species. If the results produced by Roush were to be replicated with other insect pests, there would be little possibility of managing insect resistance by planning rotations of different insecticides over time AFTER resistance had set in. In other words, ICM and IPM strategies could only be expected to work if Bt was not massively commercialised either as an exterrnal spray or asd an engineered genetic construct. If multiple resistance were also to stabilise, the future of Bt as a useful insecticide will be rather short.

U.Rahardja threw further light on the stability of insect resistance in **"Inheritance of Resistance to Bt tenebronis Cry111A endotoxin in Colorado Potato Beetle"** published in the Journal of Economic Entomology Vol 88 No 1 1995. He showed that resistance was conferred by incompletely dominant genes. Without exposure to Bt, resistance started to decline from 200 fold after 5 generations and went down to 48 fold after 10 generations. The resistance was then maintained after 12 generations up to the end of the experiment which studied 17 generations. Rahardja thus added detail to the Roush (1995) contribution, by showing that after an initial decline in resistance, subsequent generations maintained a high level of resistance even in the absence of any contact with Bt. Once resistance has set in, it appears to be permanent.

The contribution by **J. Tang** marked the beginning of a new-found pessimism regarding the future of Bt In **"Consequences of Shared toxins in Strains of Bt for resistance in Diamondback Moth"** in Resistant Pest Management Vol 7 No 1 1995 he showed that the use of Bta where resistance to Btk has developed may provide control via the Cry1C and/or Cry1D toxins, but at some cost to resistance management because resistance to Cry1A was maintained. This cost was exacerbated by the fact that resistance to Cry1A toxins could stabilise, thus making it impossible to use Btk even occasionally. The contribution by Tang marked a new phase in Bt research, where the entomologists started asking desperate questions in the search for some way of managing resistance to Bt. Every short term solution has turned out to have a long term cost and the significance of this research is that it begins to attach more importance to short term solutions than long term costs. In other words, the paradigm had now shifted from asking how Bt could be managed as a useful pesticide into the future, to a much more specific question which simply asked what we can get out of Bt whilst it still works.

Reporting on a field study in **"Stable Resistance to Bt in Plutella xylostella"** published in Resistant Pest Management Vol 7 No 1 1995, **J. Tang** showed that resistance in diamondback moths from the field was more than 1500-fold higher than normal. This declined significantly over three generations and then stabilised at between 150 and 300 fold for the next seven generations. This suggested that there could be multiple resistance alleles even when the same gene is involved. Tang had shown that the basic models no longer sufficed to explain the empirical variance.

In 1995 **Fred Gould** reported on laboratory experiments in the **"Selection and Genetic Analysis of a H. virescens Strain with High Levels of Resistance to BtToxins"** published in the Journal of Economic Entomology Vol 88 No 6 1995. Tobacco budworms were fed a diet containing the Cry1Ac Bt protein. After 19 generations the survivors developed a resistance more than 500 times the normal. Further selection led to larvae which were 10,000 times more resistant than the normal population. These larvae were resistant to Cry1Aa, Cry1Ab and Cry1F as well as the Cry1Ac protein and were partly resistant to Cry1B, Cry1C and Cry11A proteins. Perhaps with hindsight it will be this paper by Gould that marks the beginning of the end of Bt. The experiment showed that insect resistance to a toxin could climb to 10,000 times the normal and could also convey resistance to seven other toxins. If the companies currently marketing Bt crops end up dominating the market - as seems quite likely in the USA - then there is every reason to expect these laboratory results to be replicated in the field, simply because the selection pressure that was created in the laboratory will have been replicated in the fields.

J. Muller-Cohn bucked the trend in 1996 by questioning once again whether resistance to Bt was stable. In **"Spodoptera littoralis Resistance to Cry1C and Cross-Resistance to Other Bt Crystal Toxins"** published in theJournal of Economic Entomology Vol 89 No 4 1996 he reported that after 14 generations of exposure to Cry1C the spodoptera grubs were from 10-500 fold more resistant and showed partial cross-resistance to Cry1D, Cry1E and Cry1Ab toxins. Resistance declined from 500 fold to 74 fold after one generation without selection pressure and fell to 11 fold after 8 generations.

In 1996 **J. Zhao** reported the inevitable consequences of a massive military style application of Bt on cotton in **"Resistance monitoring of H. armigera to Bt in North China"**published in Resistant Pest Management Vol 8 No 2 1996. Resistance of the cotton bollworm to all chemical insecticides from 1992-95 led to the application of Bt, (which has often been used for the very first time under the threat of total crop failure.) One thousand tons of Bt (5% of the total Chinese production) were applied to 160,000 hectares of cotton in 1994 in the form of 4-6 sprays over the season. The research concluded that "the potential of H. armigera resistance to Bt toxins is most threatening to the use of both Bt formulations and transgenic Bt cotton.".

The same conclusion was reached by **J.Shen** in **"Early Detection of Resistance to Bt in H. armigera in China"** also published in Resistant Pest Management Vol 8 No 1 1996. He studied field resistance after Bt was sprayed up to 4 times per season on cotton. "It is absolutely necessary to restrict the use of conventional Bt to a maximum of 2 sprays per season in north China as a precaution against Bt resistance development in H. armigera." There is, however, no evidence that restricting Bt use to two sprays per season will really slow down the increase in insect resistance.

Meanwhile, **Y.Liu** reported the development of **"Field-evolved Resistance to Bt Toxin Cry1C in Diamondback Moth"** in the Journal of Economic Entomology Vol 89 No 4 1996. The study confirmed the spread of resistance to the Cry1C toxin which was previously effective against insects resistant to Cry1Ab found in Btk. Another weapon in the Bt armoury had thus fallen to the diamondback moth, confirming an acceleration in the phenomenon of multiple resistance.

In the name of sociological realism **D. Alstad argued,** controversially that the most useful application of Bt was simply to use it to control insects now and forget about refuge options. In **"Implementing Management of Insect Resistance to Transgenic Crops"** published in AgBiotech News Vol 8 No 10 October 1996, he proposed that any trade-off between pest control now and delaying resistance in the future should focus on the now because growers would not willingly adopt refuge strategies and they would therefore not work. His proposal was tempered by an apparently happy correlation between the preferential behaviour of corn-borers and the economic interests of farmers. See the explanation and reply from Ives below.

In response to Andow, **A. Ives** published the **"Evolution of Insect resistance to Bt-transformed Plants"** in Science Vol 273 6/9/1996. He argued that "a critical feature of corn-borer natural history is its preferential migration into the most mature stands during the first of its two annual generations. Alstad and Andow state that resistance evolution can be delayed by using Bt toxic plants in the preferred crop, thus creating a "trap crop". Because preference biased migration concentrates insect densities it increases density-dependent mortality and reduces insect abundance. The improvement Alstad and Andow attribute to the "trap-crop" strategy is actually caused by preference-biased migration itself........Changing the distribution of toxic plants among fields is not a silver bullet to combat resistance evolution."

In 1997 **Fred Gould** showed that the statistical assumptions regarding the naturally occurring resistance to Bt in the field had been hopelessly optimistic. In **"Initial frequency of alleles for resistance to Bt toxins in field populations of Heliothus** virescens"published in Proceedings of the National Academy of Sciences pp 3519-3523 April 1997 he pointed out that the rate at which a pest adapts to a toxin depends on the initial frequency of resistant genes in normal field populations. Because there was no empirical information on this frequency, all predictions regarding the spread of resistance had been based on speculative assumptions. His field research found that the natural frequency of resistant alleles was 1.5x10-1, higher than had been expected. "This high initial frequency underscores the need for caution in deploying transgenic cotton to control insect pests." When statistical assumptions are based on guesswork they seem always to err on the side of optimism. When the assumptions are eventually tested against empirical realities, the truth is often rather sobering. Gould showed that the statistical likelihood of resistance setting in the field was very much higher than had been hoped.

In the same issue of the same publication **Bruce Tabashnik** contributed an article about **"Seeking the root of insect resistance to transgenic plants"**(pp 3488-3490). He wrote that "excitement about the prospects for Bt-expressing transgenic plants and increasing knowledge about the genetics and mechanisms of resistance to Bt must be tempered with an admission of ignorance. Although many tactics have been proposed for delaying insect resistance to transgenic plants, none have been tested rigorously in the field. Nothing will be gained and much will be lost if we pretend to know more about resistance management than we really do. A lesson in the pitfalls of overzealous promotion occurred last summer when some growers found that Bt cotton did not adequately control the bollworm Helicoverpa zea." In fact, previously published data from Monsanto had shown that the Cry1Ac protein in the Bt cotton was effective against Heliothis virescens but not effective against Helicoverpa zea. This did not stop Monsanto, the manufacturers, from stupidly and dishonestly calling their product ‘Bollgard’ which led most cotton growers to think that the Bt cotton controlled the cotton bollworm, Helicoverpa zea rather than the tobacco budworm, Heliothis virescens. Had Monsanto marketed their Bt cotton as 'Budgard' there might have been less panic and less confusion.

No doubt under instructions to come up with a solution to the Bt disaster with cotton in Northern China in 1994 (see above) **J.Zhao** sought a solution in gene pyramiding. In **"Gene pyramiding: an effective strategy of resistance management for H. armigera and Bt"** published in Resistant Pest Management Vol 9 No2 1997 he explored the use of multiple toxin genes in tobacco plants, concluding that this approach could delay resistance development. Whilst it is possible that Bt pyramiding works better against some insects than against others, the contradictory conclusions drawn by Zhao and Liu simply show that much more research is needed.

In Hawaii farmers had different problems. **Y.Liu** reported on the **"Genetic basis of diamondback moth resistance to Bt toxin Cry1C"** in Resistant Pest Management Vol 9 No 2 1997. A field population of diamondback moths in Hawaii was found to have at least one recessive mutation conferring resistance to Cry1A toxin as well as genes that confered partially dominant resistance to Cry1C toxin. The dominance of resistance could vary amongst Bt toxins for a single population and the given toxin could vary among populations from different locations. This casted doubt on the effectiveness of high dose/refuge strategies which work best when resistance is recessive. Planned rotations using Cry1A then Cry1C would be a more effective insecticide strategy than use of both at once - yet another argument against pyramiding.

In December 1997 **Bruce Tabashnik** wrote **"One gene in diamondback moth confers resistance to four Bt toxins"**in Proceedings of the National Academy of Sciences Vol 94 and demolished the pyramid strategy for countering insect resistance in the very title of his contribution. He pointed out that any attempt to delay resistance to Bt by using two or more Bt toxins assumed that independent mutations were required to counter each toxin. It was also generally assumed that resistant alleles were rare in target populations. His research showed that a single autosomal recessive gene conferred extremely high resistance to no less than four different Bt toxins - Cry1Aa, Cry1Ab, Cry1Ac and Cry1F. "The finding that 21% of the individuals from a susceptible strain were heterozygous for the multiple toxin resistant gene implies that the resistance allele frequency was 10 times higher than the most widely cited estimate of the upper limit for the initial frequency of resistant alleles in susceptible populations. These findings suggest that pests may evolve resistance to some groups of toxins much faster than previously expected." This was another nail in the Bt coffin, showing that scientists had consistently underestimated the number of resistant insects in the field, and wrongly assumed that separate mutations were required for resistance to each Bt toxin. It was becoming clear that much of the original hype about what Bt could do was based on little more than wishful thinking aided by corporate propaganda machines.

Also in 1997 **U.DiCosty** returned to the dilemma posed by Whalon in 1994. The **"Selection of Colorado Potato Beetle Resistant to Cry3A on Transgenic Potato Plants"** published in Resistant Pest Management Vol 9 No1 1997, showed that "laboratory selected, highly resistant beetles could survive on Bt transgenic plants for a short period of time. If alternative host plants were encountered after selection, beetles could survive. Conversely, successive generational exposure to transgenic plants resulted in 100% mortality of this resistant strain within three generations." This article gave rise to the hope that Bt plants could be effective where the use of conventional Bt sprays had already resulted in insect resistance. However, it also questioned the effectiveness of refuge strategies.

The supposedly ‘green’ or ‘ecological’ image of Bt as the great alternative to chemical pesticides was rather tarnished by **O. Sarnthoy** in **"Cross-resistance of Bt resistant population of diamondback moth"** published in Resistant Pest Management Vol 9 No 2 1997. He recommended the use of conventional insecticides and a range of different Cry toxins to retard or reverse the development of resistance to Delfin, a Bt product produced by Novartis. The moral is rather simple: the more successful a company is at dominating the market with its pesticide product, the less time its product is likely to be biologically effective. Where the trade-off lies between massive short-term sales and moderate long term sales is a question of economics rather than entomology, though the consequences are clearly ecological.

In 1999 Y. Liu and B. Tabashnik brought the highdose/big refuge strategy for delaying insect resistance into question with a short contribution in Nature (Vol 400 p 519) which reported that insects feeding on Bt plants matured later than insects fed a normal diet. This cast doubt on the degree to which resistant and non-resistant insects might be able to breed. Interbreeding of the insects feeding on the Bt crop and the insects feeding on the refuge is necessary for the delaying strategy to work.

There is a considerable scientific literature on insect resistance to Bt sprays and Bt plants and the demonstrated facts are as follows:

1. All target insect pests have developed considerable resistance to both Bt sprays and Bt plants under laboratory conditions.
2. Some target insects have developed stable resistance to Bt sprays in the field.
3. Although entomologists are agreed that it is only a matter of time, no one has yet identified target insects that have developed resistance to Bt crops in the field.

The lack of any firm evidence of insect resistance to Bt crops in the field has led some companies - and in particular, Novartis - to claim that Bt sprays are more likely to result in resistant insects than Bt crops. But as Crawley points out in Nature (‘Bollworms, genes and ecologists’ in Nature Vol 400 pp 501-502) ‘ ...you cannot prove a negative, and absence of evidence is not evidence of absence.’

2.5 The Problem of Identifying Resistance in the Field

There are real problems in identifying Bt resistant insects and even greater problems in interpreting the evidence, given that a proportion oif all insect populations are naturally resistant to Bt. If a target insect is found eating a Bt crop there are at least five possible explanations of the phenomenon.. According to Purdue University Extension entomologist Larry Bledsoe, some crop damage is to be expected even in genetically modified crops. "No bag of Bt seed is pure. No quality control can manipulate the amount of control in each plant," he says. "If a farmer was in a field and found a couple of plants being chewed up by corn borers, that would be normal."

Here are the possible explanations:

1. Typical seed lots of Bt-maize contain a small amount - less than 4 percent - of plants that produce little or none of the protein. "This means that a few plants aren't expressing the Bt gene. That's to be expected," Bledsoe says.
2. Another explanation for finding corn borer caterpillars in resistant corn may lie in where the Bt-corn is planted. "If you plant next to a field with no resistance, some of those corn borers are going to come into the resistant field and feed along the edges for a while before they are killed," Bledsoe says.
3. A third reason for corn borers in resistant corn is that the amount of resistance in the plants isn't consistent through the growing season. "There's a slow loss of resistance in

the plant," Bledsoe says. "It's very strong at the beginning of the season, but later in the season the amount of resistance drops."
(This is particularly the case with the Novartis Bt 176 maize, which expresses practically no Bt poison towards the end iof the season.)

4. The fourth reason why a farmer might find corn borer caterpillars in the corn is that a new strain of Bt resistant corn borers have evolved in that area. According to Bledsoe, ‘There have been more than 500 examples of insects that have developed resistance to various chemical insecticides, and widespread overuse of genetically enhanced crops could cause the same thing to happen with those control methods.
To date there are no known incidents of corn borer developing widespread resistance to Bt crops in the field, but scientists know that it is possible, because resistant corn-borers have been bred in the laboratory.’
5. The fifth possibility is that the insect is one of those that are naturally resistant.

2.6 Strategies for the Management of Resistance

Entomologists and population geneticists have been experimenting with methods designed to slow down the evolution of pesticide resistance in Bt for the past eight years. According to McGaughey and Whalon (1992) there are at least 15 possible tactics for slowing down insect resistance to Bt:

A. Gene Strategies	1. single gene
	2. multiple gene
	3. chimeric genes
B. Gene Promoters	4. constitutive
	5. tissue-specific
	6. inducible
C. Gene expressions	7. high dose
	8. low dose
	9. mixture
D. Field tactics	10.uniform single gene
	11.mixture of genes
	12.gene rotation or sequencing
	13.mosaic planting
	14.spatial refuge
	15.temporal refuge

"The possible tactics for resistance management include many options. None offer clear advantages in all environments and with all pests, except, perhaps, tactics that encourage survival or immigration of susceptible genotypes. Regardless of the approach used, resistance management becomes very complex where tactics must be co-ordinated against a pest on more than one crop or against more than one pest species."

According to Gould (1995) there are now at least five different strategies being proposed:

"(1) Constitutive expression of high levels of single toxins in all plants
(2) Constitutive expression of high levels of two or more toxins in all plants
(3) Spatial or temporal mixtures of plants having high levels of constitutive expression of one or more toxins with other plants having no toxin expression
(4) Low levels of expression of single toxins interacting with the pests' natural enemies
(5) Targeted Bt gene expression."

The first two strategies rely on making the toxin so poisonous that the pest is less likely to develop the genetic potential to overcome it. However, it is already known that certain pests targeted with Bt have the ability to develop extremely high levels of resistance and that once this resistance has developed it can transfer to other Bt strains, rendering several of them useless. It is also known that the Novartis
Bt 176 maize that has been grown commercially in the USA, Germany, France, Spain and Portugal is unable to express high levels of toxin in all plants, expresses the toxin with considerable variability over time and at different rates in different parts of the maize plant.

The second strategy only works if the genes controlling resistance are rare in natural populations, and resistance to one toxin does not confer resistance to the second or third toxin. It is now known that neither of these requirements is met by studies with the diamondback moth. In fact, multiple toxin approaches could actually accelerate the evolution of resistance to a whole group of toxins.

The third strategy relies on plants that express high levels of one or more toxins (strategies 1 and 2) that are spatially or temporally mixed with plants that do not express any toxin. The supposed advantage of this strategy is that resistant insects are likely to mate with non-resistant insects coming from the refuges of non-Bt plants. To date, laboratory studies have shown that the offspring of resistant and non-resistant insects can not survive high doses of Bt toxins. However, this is presumably because the Bt resistant insects do not possess a dominant Bt resistant gene. As and when such a gene is encountered - and Tabashnik think that it can only be a matter of time - strategies 1, 2 and 3 will no longer work for that particular insect. In the meantime, according to Gould, "The higher the number of susceptible insects produced in refuges, the more likely they are to mate with resistant individuals that develop on the Bt producing plants. If there are enough of these susceptible insects, almost all of the resistant insects will mate with them instead of mating with other resistant individuals. This should result in a dramatic decrease in the rate at which resistant individuals take over the population."

Strategies 1, 2 and 3 all require Bt plants to express a dose of Bt toxin sufficiently high to kill insects with intermediate levels of resistance. However, some of the Bt crops, and particularly the Novartis Bt-maize fall far short of this standard and according to Gould (1995) "are likely to undermine this strategy."

The third strategy is the only one that has ever been required by law. In 1996 the EPA made the planting of a refuge a licensing condition for growing Bt cotton in the USA. Farmers can choose between a 4% non-treated (organic) refuge and a 25% refuge that can be treated with any insecticide other than the Cry protein expressed by the Bt crop. It follows that the resistance management strategy only works if the insecticides used in the refuge are ineffective. The refugia strategy thus contains an internal contradiction. Those who err on the side of precaution argue for the biggest refuge. But the bigger the refuge, the more important it is to control the pest within the refuge by other means, otherwise there is no advantage in planting the Bt crop. This dilemma is inherent in the biology of the system and cannot be resolved. In 1999 the EPA toughened its policies and made Bt maize subject to similar requirements. Only Bt potatoes are now free from such licensing restrictions in the USA and this is purportedly because of the close and satisfactory working relationship between the EPA and Monsanto , which has a global monopoly of Bt potatoes.

The fourth strategy relies on a very low level of toxin which does not kill the pests so much as debilitate them, thus rendering them more vulnerable to parasites or predators. Whilst this approach has a demonstrated ecological efficacy, it has not been developed by the agrochemical industry because it can only be successfully marketed to those farmers with a sophisticated understanding of the ecological environment of agriculture - the organic farmers plus the IPM/ICM practitioners. Conventional farmers have been socialised into the military paradigm and expect an insecticide to be an effective and lethal weapon. Indeed, the military paradigm raises problems for any resistance management strategy that requires a refuge because there is a built-in farmer resistance to strategies that allow some insect pests to survive.

The fifth strategy is relies on the fact that most crops do not need comprehensive protection of the whole plant all of the time. There are many pests that feed throughout the life of a plant but only cause economic damage towards harvesting time. According to Gould (1995), "in such cases advanced techniques in molecular biology could turn on the genes for toxin production only in later stages of plant development. This would decrease the exposure of the pest to the toxin, and thus decrease the rate of resistance development." However, the art of engineering Bt plants has a long way to go before it is likely to achieve this degree of sophistication, and it is likely to prove workable only for single pest species.

In practice, the five strategies can be reduced to two:
- the high toxin(s)/refuge (military) strategy
- the low toxin marginal use (holistic/organic/IPM/ICM) strategy

In reality, the holistic strategy is not supported by the agrochemical industry and the scientific history of Bt over the past decade has thus been limited to research on the questions that arise from the military strategy and which are compatible with the commercial interests of the companies concerned. There is indeed a huge amount of research being carried out on Bt and the industry is quite right when it claims that this bacterium has been more studied than any other in the history of science. The problem is that the questions being posed are important within a very narrow paradigm which itself needs questioning, but if questioned, would probably have to be rejected.

2.7 Secondary Effects of Bioinsecticide Plants

So far we have considered the growing difficulties in the relationship between Bt sprays, Bt crops and the targetted insect pests. The ‘fact’ that Bt is harmless to most insects and to all higher vertebrates has been so repeated as a scientific mantra that it had begun to appear quite unquestionable. It should also be noted that several independent scientists who have been brave enough to question the ‘Bt mantra’ have paid dearly for their scientific curiosity. There are, nevertheless, some studies on the secondary effects of Bt and these are summarised below.

1988 Sun.M
Preparing Ground for Biotech Tests
in Science 29/10/1988 p 504
Maize was inoculated with a microbe modified to express a Bt endotoxin. The microbe normally lives in the vascular structure of the plant but the microbe containing the Bt toxin was later found in flea beetles that had fed on the maize.

1993 James.R
Btk Affects a Beneficial Insect, the Cinnabar Moth
in Journal of Economic Entomology Vol 86 No 2 1993

Field and laboratory experiments indicated that Bt used to control the western spruce budworm could also kill the cinnabar moth, a beneficial that is used to control tansy ragwort, a forest weed.

1994 Swadener.C
Bt
in Journal of Pesticide Reform Vol 14 No3 pp 13-18
Swadener cites four studies of Bt being harmful to beneficial insects and a study where Bt might be harmful to amphibians and fish. "Bt has impacts on a number of beneficial species. For example, studies of a wasp that is a parasite of the meal moth found that treatment with Bt reduced the number of eggs produced by the parasitic wasp, and the percentage of those eggs that hatched. Production and hatchability of eggs of a predatory bug were also decreased. On collards, aphis-eating flies in the family Syrphidae were reduced by Dipel (Bt) treatment. Both Bt tenbebrionis and Dipel have caused mortality of the cinnabar moth, used for the biological control of the weed tansy ragwort. Finally, Bt israelensis has caused mortality of a moth (Sybclita obliteralis) that helps controlo aquatic weeds in Florida." A variety of studies have shown that Bt applications can reduce populations of many different caterpillers and larvae beside those of target insects. This in turn is shown to affect insectivore bird populations. Bt israelensis decreases the weight of tadpoles and delays their metamorphosis and in the form of Vectobac it is acutely toxic to fathead minnows, though this may because of other ingredients in the product besides Bt.

1994 Palm.C
Quantification in soil of Btk endotoxin from transgenic plants
in Molecular Ecology Vol 3 pp 145-151 1994
Palm developed a procedure to determine the fate and persistence of transgenic Btk toxin in both the laboratory and the field to provide information on the consequences of exposure of non-target soil organisms to transgenic pesticidal proteins. Although the companies producing Bt crops are obliged by the EPA in the US and by the Ministry of Agriculture in Spain to carry out studies on the environmental fate and persistence of Bt it has not proved possible to identify any new research contracts on this issue.

1997 Hawkes.N
Ladybirds harmed in transgenic crop test
New Scientist 23/10/97
Scientists in Scotland urged caution in the introduction of genetically modified crops after discovering that they could harm ladybirds, a well known beneficial insect with an appetite for several important pests. Nick Birch and a team from the Scottish Crop Research Institute in Dundee found that female ladybirds that ate aphids that had fed on genetically modified potatoes laid fewer eggs and lived only half as long as the average. The team tested a potato plant that had been modified to produce a natural insecticide (not Bt) that discouraged aphids from feeding on them.

The team found that the modified potatoes did indeed suffer reduced attack but the 50 per cent reduction was insufficient on its own, so it was important that ladybirds also did their work.

1998 Greenpeace
Ge-maize contaminates Conventional Crops
Amsterdam/Hamburg, October 12, 1998
‘Greenpeace today published new evidence which shows that Novartis genetically engineered (GE) maize has cross-pollinated an adjacent field of conventional maize in Germany. The samples analysed were taken next to a field of GE-maize in the region of

Baden-Württemberg, in southern Germany. Greenpeace marked the GE-field with a giant X in an action a month ago. The neighbouring farmer only learnt during the Greenpeace action that the maize growing less than a meter away from his field was genetically engineered. Neither Novartis, nor the German authorities have released information about the fields of transgenic maize nor did they warn neighbouring farmers. However Novartis, in a special contract with growers of its GE-Maize, did mention that a safety zone of 200 meters is necessary to avoid cross-pollination.'

Maize cobs up to 10 meters away from the GE-field were taken by the Freiburger Institut für Umweltchemie e.V. and analysed by Gene-Scan for the foreign DNA of the Novartis' maize. Analysis indicates that the rate of cross-pollination was around 5% at the field border, 0.2% at 5 meters and 0.1% at 10 meters distance.

1998 Hilbeck.A
Impact of Bt maize on Populations of Beneficial Insects
unpublished paper from Swiss Federal Research Station for Agroecology and Agriculture
Lacewings are an important predator of many insect pests killed by Bt and they are bred for use in organic and IPM strategies. The research showed 60%-65% mortality amongst lacewing larvae fed on lepidopteran larvae reared on Bt maize.

1999 Losey.J
Bt Plants and Monarch Butterflies
Nature Vol 399 p.214
Losey showed that if pollen from Bt crops fell on the wild plants normally eaten by Monarch butterfly grubs this increased the mortality rate of the caterpillars.
It is now clear that Bt is not simply the innocent and specific bioinsecticide it was once thought to be and this has implications for its use both as a Bt spray and in Bt crops.

2.8 Position Statement by the Entomological Society of America

The implications of plant biopesticides have been discussed by the professional association of American entomologists, resulting in a restatement of the precautionary principle.

"Transgenic plants that produce insecticidal substances are, and should continue to be subjected to careful testing to ensure safety and minimise environmental risks.

Insect-resistant crop plants should be deployed in accordance with scientifically based resistance-management plans to prevent the evolution of genetically adapted insect strains.

The use of insect-resistant plants is not equally appropriate for all crops in all agricutural systems; therefore a case-by-case scientific analysis of risks and benefits should be conducted before commercial use.

To prevent evolution of resistance to transgenic plants, resistance prevention tactics should be devised before pest-resistant crops are widely and intensively deployed.

Transgenic plants, especially those that produce toxins throughout the season, could bring with them difficult challenges not experienced with externally applied insecticides.

Transgenic control of a pest in one crop could limit the food source of important natural enemies and lead to increased pest problems.

Management strategies should be developed that take advantage of the ability to manipulate the spatial arrangement of transgenic plants, thereby incorporating refuges for susceptible insects into the cropping environment.

The farm-level implementation of resistance management will face practical and social obstacles.

The wisdom of using a specific insect-resistant crop should be evaluated relative to the long-term goals of reducing pesticide use and fostering sustainable crop production systems."

2.9 Summary of the Scientific Position

None of the basic research which might have enabled scientists and policy-makers to take an informed and educated view of the benefits and risks associated with Bt crops has ever been carried out. The natural ecological niche of Bt remains a mystery. Its role in natural ecosystems remains unknown. If any basic research on the life cycle of Bt and its insect targets ever gets funded and completed we can, however, be fairly certain that we will discover a series of feedback interactions and many non-linear associations because all ecological systems are characterised by such complexities.

In the meantime, laboratory studies have demonstrated what can happen, and we thus know that there are dangers involved in using Bt in any form. However, the significance of these dangers remains largely a matter for speculation. There are no sound scientific reasons for the large scale use of Bt crops and no scientific justification for what has been taking place. There are, however, sound scientific reasons why Bt crops are likely to result in the loss of Bt as a bioinsecticide.

CHAPTER 3. THE POLITICS OF Bt IN THE USA

Commercial varieties of Bt sprays and genetically engineered Bt crops have mostly been developed and marketed in the USA. Although one of the biggest players, Novartis, is Swiss, most of their Bt development work has been carried out in the US, which is also the biggest market in the world for Bt products. Over a period of seven years from 1987 the Environmental Protection Agency took the lead in developing policy proposals. In 1994 the EPA proposed a comprehensive policy for Bt crops under the terms of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA).

3.1 PROPOSED POLICIES OF THE EPA 1987-1994

From the mid 1980s onwards, the Environmental Protection Agency received numerous inquiries concerning the regulation of plants that had been modified to produce pesticides. Public interest groups were asking for regulation whilst the genetic engineering industry was asserting that self-regulation was sufficient.

In 1987, the EPA sponsored the first conference to discuss whether transgenic plants (plant varieties developed through new biotechnology methodologies) producing pesticidal substances pose potential risks and the nature of those risks. Subsequently the EPA co-sponsored two further conferences on the same theme.

The EPA also sought advice on how best to address plant-pesticides from two scientific advisory committees at three meetings. On December 18, 1992, a Subpanel of the FIFRA Scientific Advisory Panel (SAP) was convened to review a draft proposed policy statement and to answer a series of scientific questions concerned primarily with EPA's proposed approach for plant-pesticides
under FIFRA. The Scientific Advisory Panel acknowledged its political-economic as well as its purely scientific role by suggesting that the EPA would "need to create a workable balance between effective regulatory oversight and encouragement of the development of plant-produced pesticides."

On July 13, 1993, a Sub-committee of the EPA Biotechnology Science Advisory Committee (BSAC) was convened to address a series of scientific questions concerned primarily with EPA's proposed approach for plant-pesticides under FFDCA. On January 21, 1994, a joint SAP/BSAC Subpanel was convened to address a series of scientific questions concerned with the scope of regulation under FIFRA and FFDCA and guidance for data needs for the evaluation of plant-pesticides.

These consultations resulted in the EPA proposals outlined below on "pesticidal substances produced by plants under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA)."

"Substances that plants produce to protect themselves against pests and disease are pesticides under the definition of FIFRA section 2, (i.e., if they are ". . .intended for preventing, destroying, repelling, or mitigating any pest. . .") regardless of whether the pesticidal capabilities evolved in the plants or were
introduced by breeding or through the techniques of modern biotechnology. These substances, along with the genetic material necessary to produce them, are designated plant-pesticides."

The policy statement includes four aspects:
(1) It clarifies the regulatory status of such plants under FIFRA and FFDCA of plants and plant-pesticides
(2) It states that EPA's regulatory attention will focus on plant-pesticides rather than on the plants
per se
(3) It describes the criteria EPA proposes using in determining which plant-pesticides will be subject to regulation and which will be exempt
(4) It describes EPA's proposed procedures and information needs for the regulation of testing and commercial sale and distribution of plant-pesticides.

3.1.1 Summary of Proposed Policy Under FIFRA and FFDCA

The background to the current debates about Bt plants is dealt with in some detail in the following sections 3.1.2 through to 3.1.15 in order to give an indication of the legal and administrative context.

In 1982, the EPA promulgated a final regulation under FIFRA section 25(b) that *exempted* all biological control agents, except for certain microorganisms, from the requirements of FIFRA .
EPA defined the term "`biological control agent" as "any living organism applied to or introduced into the environment that is intended to function as a pesticide against another organism
declared to be a pest by the Administrator" (40 CFR 152.3).

This exemption of biological control agents was justified by the EPA on the grounds that "the risks posed by biological control agents other than microorganisms were adequately addressed by other Federal agencies such as the U.S. Department of Agriculture's (USDA) Animal and Plant Health
Inspection Service (APHIS) and the U.S. Department of the Interior."
Although plants used as biological control agents were not specifically addressed in the 1982 Federal Register notice (they were actually science-fiction at the time), they were excluded from regulation under FIFRA through this exemption.

The EPA argued at this time that the actual plants used as biological control agents were adequately regulated by other Federal agencies. However, it slowly became clear that the status of the pesticidal substances produced by plant pesticides required regulatory clarification. Ten years later the EPA justified its change of policy as follows: "Although plants used as biological control agents were excluded from FIFRA regulation under 40 CFR 152.20, substances that are extracted from plants and used as pesticides are not similarly excluded. For example, chrysanthemums produce pyrethrum, a substance that has insecticidal activity. The chrysanthemum plants that produce pyrethrum have been exempted from regulation when used as biological control agents (i.e., living chrysanthemums), but pyrethrum itself, as the pesticide substance, has not been exempted when extracted from chrysanthemums and applied to other plants as an insecticide.This distinction is reasonable in light of the potential for increased and unique exposures due to large-scale application of extracted pyrethrum to plants that do not naturally produce it. The use of extracted pyrethrum as an insecticide can involve exposure to the pesticide over large acreages, whereas the exposure associated with pyrethrum in living chrysanthemum plants would not be expected to reach such proportions. In addition, application of pyrethrum beyond the environment in which it is normally produced (i.e., beyond the living
chrysanthemum plant) could result in new or unique exposures of nontarget organisms, including humans. Although it has been EPA's policy under FIFRA to regulate pesticidal substances extracted from plants, EPA has not, thus far, clearly stated its policies for regulation of pesticidal substances
that are produced in living plants but not extracted from the plants (plant-pesticides)."

The 1992 policy statement clarifies the regulatory status of :
1.pesticidal substances that have evolved in plants,
2.pesticidal substances introduced into plants by breeding,
3.pesticidal substances introduced into plants through biotechnology.
Similarly under FFDCA, the EPA has regulated substances that are extracted from plants and used as pesticides on food or feed. For example, a tolerance has been set for pyrethrum that is extracted from
plants and applied to food or feed. However, the Agency had not specified how pesticidal substances produced in plants (plant-pesticides) would be regulated under FFDCA. For example, if a food plant were modified, for pesticidal purposes, to produce pyrethrum, EPA had not explained how this pyrethrum would be regulated under FFDCA.

3.1.2 Definitions under FIFRA

The 1992 regulation on plant pesticides proposed the following:
1. The substances plants produce to protect themselves against pests and disease are pesticides under the FIFRA section 2 definition of "pesticide," i.e., if they are ". . .intended for preventing, destroying, repelling or mitigating any pest."
2.The genetic material necessary for the production of those substances are designated by EPA as plant-pesticides.
3. The definition of pesticide under FIFRA section 2 also includes "plant regulators."
4. TheEPA proposes to focus its regulatory attention on the plant-pesticide and not on the plant per se.
5. The EPA establishes the scope of regulation for plant-pesticides under FIFRA .
6. The EPA establishes the scope of regulation for plant-pesticides under FFDCA, and proposes to regulate those plant-pesticides that have the greatest potential for new dietary exposures.
7.Recognizing the unique characteristics of plant-pesticides, the Agency proposed the establishment of a new part 174, in 40 CFR under FIFRA for plant-pesticides, with a commitment to stating procedural requirements for plant pesticides in the future.
8.In this proposed policy statement, EPA provides information on how manufacturers, importers, and distributors of plant-pesticides subject to FIFRA and FFDCA requirements should interact with the EPA, including:
(1) Information on when and how manufacturers should first consult with the Agency
(2) a set of ``points to consider'' to assist manufacturers in developing data for review
(3) descriptions of proposed Agency procedures for Experimental Use Permits (EUPs) and registration
(4) descriptions of EPA's interaction with other agencies.
US pesticide legislation is summarised in Annex 5.

3.1.3 Definition of a Plant Pesticide

"A pesticidal substance that is produced in a living plant and the genetic material necessary for the production of the substance, where the substance is intended for use in the living plant."

The EPA justified the inclusion of the genetic material in the definition as follows:
"First, it is the genetic material that is introduced into the plant with the intent that it will ultimately result in a pesticidal effect. Additionally, EPA's regulation of pesticides is based on an
evaluation of the potential for unreasonable adverse effects to humans and the environment associated with the use of the pesticidal substance, in this case, the pesticidal substance produced in the
plant. Regulation also includes risk management considerations. A focus on the genetic material would permit the Agency to address the potential for the spread of the pesticidal substance in the environment
through the spread of the genetic material necessary for the production of the substance. Moreover, the amount of pesticidal substance likely to be produced by the plant is also an important consideration that the Agency may, in some circumstances, be able to address through the inclusion of genetic material in the definition of plant-pesticide. In addition, including the genetic material in the definition of plant-pesticide would permit the Agency to address plant-pesticides during stages of the plant's life cycle or in plant parts where the pesticidal substance itself is not produced or is produced in very small

amounts (e.g., in pollen or seed). In these cases, it is technically easier to verify the presence of the genetic material than the pesticidal substance.

The regulation of pesticides under FIFRA entails the identification of "active ingredients" and "inert ingredients." Under FIFRA section 2, the term active ingredient means ". . .an ingredient which will prevent, destroy, repel, or mitigate any pest. . . [or acts as a plant regulator, defoliant or desiccant]."

The term inert ingredient means ". . .an ingredient which is not active." EPA recognizes that plant-pesticides have certain characteristics that are different from those of more traditional chemical pesticides. EPA believes that the overall characteristics of plant-pesticides require specifically tailored active and inert ingredient definitions.

In light of this consideration, EPA proposes to use the following definitions for active and inert ingredients for plant-pesticides.

`Active ingredient," when referring to plant-pesticides only, means a pesticidal substance that is produced in a living plant and the genetic material necessary for the production of the substance, where the substance is intended for use in the living plant.

`Inert ingredient," when referring to plant-pesticides only, means any substance, such as a selectable marker, other than the active ingredient, and the genetic material necessary for the production of the substance, that is intentionally introduced into a living plant along with the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient.

Note that the plant-pesticide active ingredient is the plant-pesticide and therefore the proposed definition of active ingredient for plant-pesticides is the same as the definition of plant-pesticide.

The plant-pesticide product includes both the active and inert ingredients.

The definition of plant-pesticide and the active and inert ingredient definitions would include all of the genetic material ``necessary for the production'' of the pesticidal and inert substance. The following genetic regions are considered ``necessary for the production'' of the plant-pesticide, active and inert substances:

(1) The genetic material that encodes for a pesticidal substance or leads to the production of a pesticidal substance and

(2) regulatory regions such as promoters, enhancers, and terminators.

3.1.4 Definition of a Plant Regulator

A substance that is produced in a plant as a result of a change in the plant's physiology would be considered a plant regulator if:

It is intended to accelerate or retard the rate of growth or rate of maturation, or alter the behavior of the plants and meets one of the following criteria:

(1) Is a plant hormone.

(2) Acts to prevent, destroy, repel, or mitigate a pest.

(3) Is toxic in concentrations found in the plant (undiluted package).

A few examples of substances expressed in plants that would not be considered plant regulators and therefore not under EPA's authority are:

(1) Substances intended to alter the nutritional composition of the plant;

(2) substances intended to enhance the plant's resistance to chemical herbicides; and

(3) substances intended to alter the flavor or the texture of the food.

3.1.5 The Regulatory Process Under FIFRA and FFDCA

This section outlines the process EPA proposed following for plant-pesticides subject to FIFRA and/or FFDCA requirements. It describes the options that EPA was evaluating for its approach to the regulation of testing of plant-pesticides and included the current proposed Agency's thinking for sale or distribution of a plant-pesticide. For the future, EPA proposed regulations concerning the procedures for plant-pesticides under FIFRA (e.g., EUPs and labeling). This step by step approach created ceratin anomalies that were clear to the EPA:

‘In the period before procedures that are specific for plant-pesticides are finalized, existing regulations will be used as the basis for plant-pesticide regulatory procedures. However, the Agency is aware that many of these existing procedures may not be appropriate for plant-pesticides, and encourages producers to contact EPA on a case-by-case basis.’

‘Producers of plant-pesticides should be aware that having no obligations under one of the statutes (FIFRA or FFDCA) does not necessarily mean that there are no obligations under the other statute.

Producers should therefore evaluate the requirements of both statutes before reaching a determination on their responsibilities.’

‘Producers should also be aware that if certain plant-pesticides present unreasonable risk and there are limited or no risk mitigation options available to the Agency for certain plant-pesticides submitted for registration, the Agency would not be able to register the plant-pesticides. Potential registrants are again encouraged to consult with EPA for guidance early in the product development cycle.’

3.1.6 Testing of Plant Pesticides (1992)

The following section outlines the EPA's preferred approach as to when a producer should contact EPA under FIFRA and FFDCA during testing of a plant-pesticide. The procedures were laid out in terms of whether the crop would be used as food and/or feed since this question is among the first considerations in determining when to contact EPA.

1. Food and/or feed use. This unit gives guidance as to when a producer would have obligations under FFDCA and FIFRA if a plant-pesticide is tested in a crop/plant used for food and/or feed or if any adjacent food/feed plants would produce the plant-pesticide.

a. FFDCA requirements. The FFDCA requirements for a plant-pesticide would be based on the following considerations.

(i) Existing exemption from the requirement of a tolerance. If there is an existing exemption from the requirement of a tolerance for the plant-pesticide in the crop/plant to be tested (e.g., if EPA's proposed tolerance exemptions published elsewhere in todays issue of the Federal Register), there would be no further obligations under FFDCA.

(ii) Containment. A tolerance review would not be required for the test if the crops/plants containing the plant-pesticide are tested in a way that ensures adequate containment within the test site of the genetic material necessary for the production of the pesticidal substance. ``Adequate containment'' in this context would include ensuring any adjacent crops, to be used as food, do not express the plant-pesticide as a result of successful pollination by the plant used to test the plant-pesticide.

(iii) Crop destruct. A tolerance review would not be required for the test if all crops within the test site are destroyed or used for experimental purposes only.
(iv) Petition for temporary tolerance or exemption. If there is no existing exemption from the requirement of a tolerance for the plant-pesticide, if containment is not adequate or the crop is not destroyed, a petition for a temporary tolerance, a full tolerance, or an exemption from the requirement of a tolerance must be submitted to the Agency, as described at 40 CFR 180.7 and 180.31. Such a crop cannot be sold or distributed for use as food or feed unless a tolerance or exemption from the requirement of a tolerance has been obtained for the plant-pesticide in that crop and the plant-pesticide residues fall within the tolerance limits.
b. FIFRA requirements. Prior to registration, if a plant- pesticide is produced in a crop/plant that is to be used as food or feed (condition (iv) above) at any field test acreage, producers would apply for an Experimental Use Permit (EUP) for that plant-pesticide under FIFRA.
2. Nonfood and nonfeed use. This unit describes when a producer would have obligations under FFDCA and FIFRA if the plant-pesticide is used in a crop or plant that will not be used for food and/or feed.
a. FFDCA requirements. If a plant-pesticide is produced in a crop/plant that will not be used as food and/or feed, there would be no requirements under FFDCA as long as the genetic material is adequately contained to avoid successful transfer and expression of the plant-pesticide in adjacent crops. (Refer to Unit V.A.1.a.(ii) and (iii). above for conditions of containment and crop destruction under which there are no FFDCA requirements.)
b. FIFRA requirements. If a plant-pesticide is produced in a crop/plant that will not be used as food and/or feed, an Experimental Use Permit would be required under the following conditions.

(i) Not subject to the Plant Pest Act. If a plant-pesticide is produced in a plant that is not subject to the authority of the Plant Pest Act, an EUP would be required at first field introduction. This EUP requirement would extend to plant-pesticides in plants that are not within the statutory jurisdiction of the Plant Pest Act, including those for which APHIS has made a determination of nonregulated article status (58 FR 17044).

(ii) Acreage requirements for plant-pesticides in plants subject to the Plant Pest Act. For plant pesticides produced in plants that are
(1) subject to the authority of the Plant Pest Act and
(2) not used as food or feed, an EUP would be required when one of the following two conditions is met.
(A) Acreage limit for individual field test. An EUP generally would be required if an individual field test for a plant-pesticide in a particular crop will be on greater than 10 acres of land. Once a requirement for an EUP has been triggered, if there are other field test site locations, for that plant-pesticide, of less than 10 acres that would also be planted in the same year, they would be included in the EUP. If a field test site of greater than 10 acres is planted for a crop that is producing more than one plant-pesticide, all field test sites for each of the plant-pesticides would be included in the EUP if these field tests would occur in the same year.
(B) Upper cumulative acreage limit for field tests. Notwithstanding (A) above, an EUP would be required if the cumulative acreage of all field tests for the plant-pesticide in a particular crop exceeds 50 acres of land regardless of the acreage of individual field sites.

(iii) Other conditions for EUPs. The Agency could grant multi-year EUPs for plant-pesticides under certain conditions. For example, a multi-year EUP could be appropriate if the acreage of the field sites
will increase yearly but the field test design and containment measures for the field sites remain the same such that there is not an increased risk for nontarget effects or outcrossing. In addition, producers
should be aware that the data requirements for an EUP may not be different from the data requirements for a registration of the plant-pesticide.

3.1.7 Regulation of the Sale or Distribution of Plant Pesticides (1992)

1. FFDCA. If a plant-pesticide is produced in a crop to be sold or distributed as food and/or feed and is not already exempt from the requirement of a tolerance, the Agency must establish a tolerance or exemption from the requirement of a tolerance before sale or distribution.
2. FIFRA. Before sale or distribution of a plant-pesticide, a producer would have to obtain a registration for the plant-pesticide product, unless it is otherwise exempt, as described in this document (Unit VI.B. of this document). The plant-pesticide product consists of the active ingredients and inert ingredients, as defined in Unit IV.B. of this document, EPA anticipates that the plant-pesticide product would be registered for use in a particular plant or crop (e.g., field corn). While the Agency anticipates that most registrations of plant- pesticides would be for use in a particular plant or crop, there may be instances where a registration of a plant-pesticide could be limited to a particular variety or be restricted in some other way if risk considerations warrant such a restriction. In terms of shipping, EPA does not intend to change the status of the exemption under section 12(b)(5) of FIFRA which allows the shipping of a pesticidal substance under the conditions of section 12(b)(5) without being subject to penalty for failure to have a registration or EUP.

3.1.8 Regulation of Field Tests (1992)

‘1. Agency considerations underlying FFDCA regulatory procedures.
Under FFDCA at the field testing stage, the Agency will generally treat plant-pesticides as it treats other pesticides in terms of when EPA regulatory oversight begins. Thus, producers will be subject to FFDCA requirements when the crop plant containing the plant-pesticide is to be used as food or feed. EPA recognizes that many of its requirements for addressing feed under FFDCA arise because some pesticidal substances may be metabolized or stored by domesticated animals in ways that expose humans to these pesticides and/or their residues through consumption of meat or other animal products (e.g., milk and eggs). EPA also recognizes that the possibility that consumers might be exposed to proteinaceous plant-pesticides through such animal products is extremely low. Proteinaceous plant-pesticides are likely to be composed of the same constituents as animal protein or other animal cellular components, and, thus, would readily enter the metabolic cycles of the animal cell. For proteins, it is not anticipated that recalcitrant residues will be generated or accumulated in animals used as sources of meat. However, EPA cannot predict that all plant-pesticides will behave as proteinaceous plant-pesticides. Thus, EPA will require plant- pesticides to be subject to FFDCA when the plants producing the plant- pesticide are used as feed. Data requirements associated with the tolerance review will, however, be imposed recognizing the characteristics of proteinaceous plant-pesticides.’

‘2. Agency considerations underlying FIFRA regulatory procedures.
The following unit describes EPA's rationale for its preferred trigger for EUP's and describes alternative approaches to the EUP trigger EPA is considering. The preferred approach and the alternative approaches address testing of plant-pesticides that are subject to the Plant Pest Act and are not used as food and/or feed. EPA believes some type of oversight of plant-pesticides at the field testing stage is appropriate. Plant-pesticides are, by definition, part of a living organism. Thus, plant-pesticides present unique mechanisms by which they can be produced and spread in the environment. Because of the different risk considerations and risk mitigation measures associated with plant-pesticides than with traditional chemical pesticides, EPA is examining whether the 10 cumulative acre presumption in 40 CFR 172.3 is appropriate with regard to plant-pesticides. Potential risks associated with tests of plant-pesticides will depend upon a number of variables, including the size of the test plot, the biology of the plant and the properties of the pesticidal substance. At smaller acreages, tests of plant-pesticides can usually be designed with containment that is adequate to minimize the spread of the plants' genetic material beyond the test site, thereby limiting the spread of the active ingredient from the field test site. Successful containment of the genetic material would result in minimal exposure of humans and other nontarget organisms to the active ingredient beyond the test site. During the development of plant-pesticides, depending upon the biology of the plant tested and the location of the field test sites, there will be a point at which it will be impractical to try to contain the spread of the genetic material. In terms of risk, the Agency believes its oversight of plant-pesticides under FIFRA should begin at the point when containment is impractical and the potential for significant exposure to nontarget organisms begins to increase. As tests of plant-pesticides progress to larger acreages, the potential hazards to nontarget organisms will generally be increased because of the potential for significant exposure to nontarget organisms on the test site. In addition, lack of adequate containment may mean the spread of the active ingredient and subsequent possible environmental exposure beyond the test site. Moreover, if the active ingredient is spread to neighboring crops used for food and/or feed, human dietary exposure could occur. Under any of the options put forth by EPA for EUP thresholds for plant-pesticides, EPA would retain the authority to rebut the presumption that an EUP is not required for certain small-scale testing. Such a rebuttal would be based on risk/benefit considerations. Thus, EPA may, on a case-by-case basis require EUP's for testing conducted with plant-pesticides at acreages smaller than those described in the options. EPA does not anticipate requiring EUP's at acreages below the threshold triggering EUP requirements (regardless of which option is chosen) very often, and when EPA determines that such an EUP is warranted, EPA will provide notice to the producer of the plant-pesticide being tested. In addition to risks in terms of hazard and exposure, EPA considered the following in developing its options for the threshold for EUPs for plant-pesticides:
(1) Differences in the traits of plant- pesticides (e.g., the delivery system of the pesticide in that plant- pesticides are produced and used in a living plant) in comparison to more traditional chemical pesticides (e.g., they are applied to a plant);
(2) varietal development procedures used in the plant breeding industry and the impact this has on the design of field testing;
(3) USDA's activities under the Plant Pest Act for transgenic plants (some of which will be engineered to express plant-pesticides);
(4) clarity to the regulated and other communities;
(5) EPA's traditional approach to oversight of field testing in terms of establishing acreage cutoffs so as to provide regulatory consistency; and
(6) costs to potential registrants and efficient utilization of Agency resources.

a. EPA's preferred approach: single-site acreage threshold. Under its preferred approach, the Agency would use the concept that larger acreage for individual field sites leads, in general, to greater exposures and greater potential for escape from biological containment. Therefore, the Agency would link the concept of greater exposure to an acreage cutoff (i.e., 10 acres for a single field test site, 50 cumulative acres). EPA recognizes that the acreage cutoff in its preferred approach may be more closely correlated with the potential for larger exposures for some crops than for others. However, it believes that the advantage of clarity and predictability associated with the acreage cutoff would outweigh this disadvantage. In addition, EPA would put an upper limit on the number of cumulative acres that could be planted without an EUP because multiple sites of larger acreages would lead to an increased potential for exposure to nontarget organisms on the cumulative acreage.

b. Alternative approaches for testing of plant-pesticides. EPA is also considering four alternative approaches to triggers for Agency oversight for testing of plant-pesticides, under FIFRA section 5, for plant-pesticides that are subject to the Plant Pest Act and are not used as food/feed.

(i) Containment as trigger for EUP. EPA seriously considered, and may yet choose to use as its trigger for EUP requirements, the concept of containment. Essentially, once a plant can no longer be effectively isolated biologically, EPA's EUP requirements would be triggered. To be isolated biologically means that the genetic material of the plants on the test site does not have a significant potential for successfully spreading to neighboring plants (including neighboring crop plants) through sexual recombination. The concept of biological isolation is basic to USDA's approach and use of such a standard by both agencies could permit a smooth transfer of oversight for plant-pesticides from USDA to EPA. The disadvantage of using this approach for EPA and for potential registrants, is that what constitutes ``appropriate containment'' varies from crop to crop and test to test. EPA is concerned that the lack of a clear line as a standard may result in numerous consultations between EPA and potential registrants over what constitutes appropriate containment. In addition, other groups, such as the public and public interest groups, may not be able to readily determine whether a potential registrant is in compliance with EPA requirements. Finally, there are exposure issues (i.e., larger potential for exposure on individual field sites at larger acreages) that are not addressed by this alternative.

(ii) USDA/APHIS determination of nonregulated status as trigger for EUP. A second alternative approach EPA is considering is based on USDA's determination of nonregulated article status (58 FR 17044). Under this alternative, producers would apply to EPA for an EUP (or registration) at the time that they apply to APHIS for a determination of nonregulated article status. Although this approach could potentially minimize duplicative efforts by the two agencies, it lacks regulatory clarity and consistency as to when a producer would have to comply with EPA requirements. This approach may result in producers being uncertain as to when they should contact EPA. The result of this lack of regulatory clarity could be producers applying to EPA too late in their product development cycle.

(iii) Cumulative acreage in a single state as trigger for EUP. The third alternative would be based on an acreage trigger, as is EPA's preferred approach. Under this approach, an EUP would be required when the cumulative acreage in any one state exceeds 10 acres. This alternative would allow producers to test a plant-pesticide in a number of different locales yet limit exposure to the plant-pesticide in any one locale. However, this approach also lacks regulatory clarity as to when producers must contact EPA if a number of different states are involved. Other groups, such as the public and public interest groups may not be able to readily determine whether a producer is in compliance with EPA requirements. In addition, fairly large total acreages of testing might occur since up to 10 acres could be tested in each of 50 states. The potential for exposure to

nontarget organisms and outcrossing to wild relatives could be greater with this alternative than for the preferred or other alternative approaches.
(iv) Cumulative acreage as trigger for EUP. A fourth alternative EPA is considering is to utilize for plant-pesticides the acreage presumption in the current EUP regulations; i.e., an EUP is presumed not to be required at less than 10 cumulative acres of land. The advantage this alternative presents is consistency in EPA's EUP regulations for all pesticides. The disadvantages to this approach are that it may not correlate well with current plant breeding procedures (varietal testing) that can require a number of field sites of smaller acreages and it may result in more duplicative efforts by EPA and USDA. It should be noted that EPA has not addressed in this document how it will approach aquatic testing of plant-pesticides. Producers anticipating research and commercialization activities with aquatic plants are encouraged to contact the Agency.’

3.1.9 Labeling Requirements (1992)

‘Labeling is required for pesticides that are regulated by EPA under FIFRA. Labeling includes both written material accompanying the pesticide and labels on or attached to the pesticide, its container, or wrapper. Labeling thus may have different forms. A pesticide which does not meet labeling requirements is considered to be misbranded and enforcement action can be taken.. The Agency recognizes that certain types of labeling which are appropriate for chemical pesticides will not be practical for plant- pesticides. For example, it would be impractical to require labels to be physically attached to the plant-pesticide itself (i.e., the pesticidal substance and the genetic material necessary for the production of the substance) at any point in the regulatory process (i.e., EUPs or registration). Therefore, the Agency is considering the types of labeling that would be appropriate for plant-pesticides during testing and at the time of registration. Labeling can include both prescriptive and informational components. The Agency is considering utilizing both these types of labeling for plant-pesticides. For example, plant-pesticides that are regulated by EPA but are not yet registered (e.g., are under an EUP) may have prescriptive labeling that would set forth the appropriate conditions for field testing, such as geographic location, field test design, and other limitations. The Agency believes that this type of labeling would be appropriate at this point in the regulatory process because the Agency would not have yet made a determination that the plant-pesticide generally will not result in ``unreasonable adverse effects'' without the restrictions specified on the label. Thus, the prescriptive labeling would be necessary to assure there would not be unreasonable adverse effects during the test of the plant-pesticide. Plant-pesticides that are registered would also have prescriptive labeling that would accompany the plant-pesticide throughout the process of developing and producing the commercial plant variety that contains the plant-pesticide. Such prescriptive labeling would, for example, specify the EPA registration number, the ingredient statement, and the plants/crops in which the plant-pesticide may be produced. It is unlikely, however, to include many of the limitations, discussed above, likely to be used for unregistered plant-pesticides because these types of limitations would not be practical for registered plant- pesticides. For example, limitations such as conditions for planting, field design, or certain geographical restrictions may not be practical given the nature of the use and distribution patterns of the plants that produce the plant-pesticide (e.g., farmers saving seed for replanting, the potential for spread of the plants' genetic material). In some cases it will be appropriate for the Agency to assume that, at sale or distribution, the plant-pesticide will be introduced into all plants/crops (and their varieties) that are included in the plant-pesticide registration (e.g., all corn varieties). The appropriateness of this assumption will be considered, on a case-by-case basis, by EPA in its assessment of whether a plant-pesticide produced in a particular crop/plant presents ``no unreasonable adverse effects." The prescriptive label for a registered plant-pesticide may include a provision requiring informational labeling on plants/seeds containing the plant-pesticide to give information or notice to farmers and growers of the plant-pesticide. For example, informational labeling of this type could be attached to bags of seeds and could inform farmers of the type of pesticide that the plants will produce and against which pest it is active. EPA believes that such informational labeling will help to prevent unnecessary application of additional pesticides to the plants. The prescriptive label may require that the informational labeling accompanying plants or seeds bear other necessary statements. For example, the informational label could be required to have a statement that informs farmers and growers that they should report any adverse effects to the registrant through an address or telephone number provided on the label.'

3.1.10 Import and Export Regulations (1992)

'Unregistered, exported plant-pesticides that are not exempt from FIFRA regulation will be subject to the Final Export Policy Statement. However, the Agency recognizes that some of the labeling requirements for exports may not be applicable to plant-pesticides (e.g., net weight of the plant- pesticide may be difficult to determine in some cases). EPA is also considering whether to require an informational label on exported seeds/plants containing a registered plant-pesticide that contains:
(1) Information about the type of plant-pesticide produced by the plants and the target pest, and
(2) a statement that EPA's determination for registration of the plant-pesticide is based solely on consideration of risks in the United States and that this determination does not extend to use in other countries. If an imported plant-pesticide will be used for pesticidal purposes (e.g., if the seeds are sold to be planted and the resulting plants are intended to produce the plant-pesticide), the producer must apply for a registration of the plant-pesticide under FIFRA. As with labeling for exports, certain provisions in the ``Notice of Arrival of Pesticides and Devices'' (EPA form 3540-1) may not be applicable to plant-pesticides. If a producer plans to import seeds/plants that contain a plant-pesticide, a tolerance or exemption from the requirement of a tolerance must be obtained if the plants/seeds will be used for food and/or feed. The Agency encourages producers to contact EPA with questions concerning procedures for both import and export of plant-pesticides.'

3.1.11 Sale or Distribution. (1992)

'In order to assess the potential exposure when a plant-pesticide is sold or distributed, EPA will consider whether all varieties of a crop in which the plant-pesticide is registered will be able to express the pesticidal substance. Potential exposure could also result if the plant-pesticide is expressed by plant relatives to which the genetic material encoding the plant-pesticide could be transferred. This analysis of exposure is a component in the possible identification of the types of nontarget organisms that associate with particular types of crops/plants and therefore may be exposed to the pesticidal substance. This type of analysis would be considered depending on the plant-pesticide/plant combination. In addition, sale or distribution will often involve human dietary exposure and may thus require information to address those risks and to support a tolerance or tolerance exemption.'

3.1.12 Environmental Fate Analysis (1992)

1. ‘An accurate assessment of the fate, transport, and persistence of the pesticidal gene product (pesticidal substance) in the environment is essential to the entire risk assessment process. This information will determine if there is adequate containment during product development and will support the ecological non-target species and the health effects risk assessments for sale or distribution of the products. The following environmental fate risk issues are associated with field tests and sale or distribution of a plant-pesticide:

(1) Increasing the ability of the modified plant to survive outside of cultivation through the introduction of a specific trait.

(2) Gene capture and expression of the introduced trait by a wild or weedy relative.

(3) Potential for a trait conferring a selective advantage to a plant in a natural plant community with the result of increasing the ``weediness'' of that species.

(4) Environmental fate of the pesticidal substance. The dosage to soils after plant senescence and incorporation into the soil, rate of degradation or dissipation and transport in the environment. Also whether or not the pesticidal substance is either exuded or volatilized from the plant during the growing season, resulting in a continuous application to the environment. The environmental fate of plant-pesticides introduced into the environment is composed of two facets: the movement of the gene encoding for the pesticidal substance (biological fate) and the fate of the pesticidal substance itself (chemical fate). Some of the information about the biology of the plant producing the plant- pesticide may be available in the published literature and this information should be used to address the biological fate risk issues. There are several points of information that a producer should consider when developing a plant-pesticide for sale or distribution in agriculture. The points are arranged in a tiered framework that allows for resolution of the risk issue as early as possible in the review process.

2. Biological fate analysis. The first consideration in the biological fate analysis is whether or not the plant producing the plant-pesticide can exist under other than cultivated conditions. This consideration results from risk issue above. The next consideration is whether or not the plant producing the plant-pesticide has weedy or wild relatives and whether the relatives are distributed in or near the areas where the plant will be grown. This consideration results from risk issue (2) in Unit VI.D.1. above. If the plant producing the plant-pesticide does have weedy or wild relatives of concern, the next consideration is whether, based on its life cycle, pollinator requirements, and genetic limitations, it can take part in a successful outcrossing event. If the plant producing the plant-pesticide has the ability to outcross, the next considerations are its outcrossing rate and pollen longevity under laboratory conditions. If it is determined that either or both of these factors are high, outcrossing rates should be determined under field conditions. If significant outcrossing is achieved under field conditions a determination of whether the plant-pesticide confers a selective advantage to the relative would be made.

3. Exposure to the pesticidal substance produced by the plant. If there is a toxicological concern for the plant pesticidal substance, an assessment of expression levels in all or some parts of the plant may be required.

4. Chemical fate analysis. Determining the persistence and movement of the pesticidal substance in the environment would be required if there is a toxicological concern for that pesticidal substance. Points that should be considered are the pesticidal substance's persistence and mobility in all environmental media (soil, water, and air). If the substance is persistent and another crop is grown in rotation with the transformed crop, a crop rotation study would be required. Similarly, if the pesticidal substance is stable in the

environment and is expected to reach aquatic environments, a fish accumulation study would be required.'

3.1.13 Ecological Effects (1992)

Of particular interest is the EPA assessment of ecological risks *before* Bt crops were commercialised.

'Sale or distribution of a plant-pesticide may ultimately lead to the plant-pesticide being expressed in the entire agricultural crop of the plant that is producing the plant-pesticide and in any other crops and/or relatives with which the plant can cross-breed. A careful analysis of all potential nontarget species (including threatened or endangered species) that may be susceptible to the pesticidal substance may thus be needed. Some plant/plant-pesticide combinations may not be acceptable for registration if use could be expected to result in unreasonable environmental effects if traditional risk mitigation restrictions are not appropriate for the plant-pesticide. In these cases, genetic limitations on the expression of the pesticidal substance in plants, or on the potential for gene transfer to other plants, may result in sufficient risk reduction to allow registration. Also, if the presence of the plant-pesticide is limited to the actual plant material, the number and kinds of species exposed may also be limited. EPA has, for traditional pesticides, relied on single species testing to evaluate potential effects on nontarget species, and this approach will continue to be of value. However, the standard test species and the standard acute exposure protocols used for chemical pesticides may not be sufficient to evaluate plant-pesticides due to their unique exposure scenario, e.g., the presence of the pesticidal substance as part of the plant and the potential for gene flow to other plants. In addition, the substance to be tested (whole plants, extracts of plants, pure pesticidal-substance, etc.) may have to be determined on a case-by-case basis, but the substance should be tested in an ecologically relevant manner. Unlike traditional chemical pesticides where direct contact is the predominant form of exposure, exposure to plant-pesticides will primarily be from ingestion of, or contact with, plant tissues that contain plant-pesticides. Traditional test protocols rely on a maximum-hazard dose to ensure that potential adverse effects are detected. However, it may be difficult to obtain a maximum-hazard dose using plant-pesticide materials if there are low expression levels of the pesticidal substance in the plant. Therefore, in some cases, chronic exposure testing may be more appropriate.

The following points may be of particular value in performing an ecological risk assessment:

(1) An analysis of which non-target species feed on, or contact, plant parts that will contain the pesticidal substance will be particularly helpful in identifying the species to be tested. Consideration should be given to which species are most representative of those likely exposed to the plant-pesticide. (2) If the pollen of a plant contains the pesticidal substance, the pesticide substance may be airborne beyond the immediate field location. The effect on aquatic invertebrates may need to be determined. Plant pollen enters the aquatic environment quite readily through wind movement. In addition, honeybees, and particularly honeybee larvae, are likely to be exposed to pollen. Honeybee larvae may be susceptible to these plant-pesticides, especially those intended to control insect larvae, even if the adult honeybees are resistant.

(3) If the pesticidal substance is expressed in the seed or fruit, a different range of non-target organisms will be exposed than if the pesticidal substance is produced in the pollen. In this instance, possible effects on birds and mammals should be considered.

(4) The duration of testing is a factor. If the pesticidal substance is expressed by the plant throughout the entire plant life- cycle, some nontarget species may be exposed to a

chronic dose of the substance as compared to traditional pesticide usage which often results in an acute dose. Chronic exposure in terms of the duration of expression of the plant-pesticide by the plant could be measured in terms relative to the life cycles of nontarget organisms likely to be exposed.
(5) If, after harvest at the end of the growing season, the plant tissue containing the plant-pesticide is tilled into the soil or left in the field to decompose, soil organisms (i.e., Colembola and other soil arthropods, nematodes, mollusks, and annelids) may receive a low level chronic exposure, depending on the stability of the pesticidal substance. This may affect decomposition processes which occur naturally in the soil.
(6) Threatened or endangered species may be at risk from widespread or uncontained use of the plant-pesticide. Since the pesticidal substance may have the potential to be expressed in the entire crop and related plants, it may be difficult to limit the exposure of threatened or endangered species. There is particular cause for concern if there are any threatened or endangered species related to the target species that feed on the plants or if there are any threatened or endangered species related to species susceptible to the pesticidal substance. Information on the feeding habits and preferred food sources of any potentially affected threatened or endangered species will be needed to address this issue.
(7) Secondary feeding effects may increase the possibility of non- target exposure, e.g., the possibility that species feeding on the plant would accumulate enough pesticide to affect predatory species feeding on them.
(8) The possibility of transfer of a disease- or insect- resistant trait to wild or weedy relatives or the presence of the trait in the crop, itself, may create a weed or may increase the competitiveness of a known weed. There may be cause for concern if related, naturally- occurring, pest-resistant plants are weeds, particularly if this particular pest-resistant trait is found in the most aggressive varieties of the weeds. If the pesticidal trait results in significantly greater pest-resistance, analysis of the competitiveness with naturally occurring weeds may be a practical way to address this issue.'

3.1.14 Development of Resistance to Plant-pesticides (1992)

Although Novartis was arguing until well into 1998 that Bt crops posed no insect resistance problems it is clear that the EPA was well aware of the potential nearly ten years earlier and it is also clear that Novartis was aware of the EPA position.

'EPA recognizes that there is a potential for the development of resistance to plant-pesticides. At present, the issue has been raised particularly in the case of the Bacillus thuringiensis insecticidal delta-endotoxin. Field resistance to the delta-endotoxin has been documented for foliar applications of the microbial pesticide, Bacillus thuringiensis. It is postulated that resistance to the delta- endotoxin could develop when it is produced by plants. The development of insect resistance to the delta-endotoxin could lead to a loss in the effectiveness of this valuable pesticide. EPA is committed to the development of pesticides that are viable alternatives to more toxic and persistent chemical pesticides. The Agency is considering how it can best encourage the development of agricultural practices that will minimize the development of resistance to plant-pesticides. Toward this end, the Agency has begun to analyze the regulatory and nonregulatory tools it could use to address resistance to all pesticides, including plant-pesticides.'

3.1.15 Other Agencies

EPA is the Federal agency primarily responsible for the regulation of pesticides. However, the EPA works closely with the U.S. Department of Agriculture (USDA) which has responsibilities under the Plant Pest Act and the Plant Quarantine Act and the U.S. Food and Drug Administration (FDA) which has responsibilities under the Federal Food, Drug and Cosmetic Act (FFDCA).

A. US Department of Agriculture

The USDA has the authority to prevent the introduction and dissemination of plant pests under the Plant Pest Act and the Plant Quarantine Act. An introduction at any acreage of a plant that is under the jurisdiction of the Plant Pest Act requires either that a permit be obtained from USDA's Animal and Plant Health Inspection Service (USDA/APHIS) or for certain plants that a notification be submitted to USDA/APHIS, unless it has been exempted from those requirements.

B. Food and Drugs Administration

Pursuant to FFDCA and the reorganization that created EPA, pesticides as defined by FIFRA are subject to EPA's regulatory authority under FFDCA. However, the FDA's authority under FFDCA extends to any nonpesticidal substance that may be introduced into a new plant variety and that is expected to become a component of food.
The two agencies have agreed that the EPA will address under its regulatory jurisdiction the food safety issues associated with the plant-pesticide, including marker genes used to confirm the presence of the DNA necessary for the production of the pesticidal substance. Any food safety questions beyond those associated with the plant-pesticide, such as those involving changes to food quality or raised by unexpected or unintended compositional changes, are under FDA's jurisdiction. Similarly, food safety issues associated with alterations in levels of a substance with pesticidal properties, or the appearance of a substance with pesticidal properties that occur as an unintended consequence of modifications to a non-pesticidal trait would also fall under FDA's authority..

3.2 THE EPA HEARING ON PLANT PESTICIDE RESISTANCE MANAGEMENT 21 March 1997

The EPA was forced into organising a public hearing in the wake of Monsanto's Bt cotton (Bollgard) failure to control the bollworm in July 1996, the first season it was sown. There remains a good deal of misunderstanding as to what happened in the cotton fields. Many observers continue to believe that the cotton bollworm became resistant to the Bt cotton. The truth is less alarming in biological terms but more alarming in political terms. The Bollgard Bt cotton was developed in the hope that it would control all three main pests of cotton - the tobacco budworm, the cotton bollworm and the pink bollworm. The plants failed to control the cotton bollworms from Texas to Georgia, resulting - it was thought - in the production of resistant cotton bollworms. This raised serious questions as to the potency of the Bt plants, and whether Monsanto's resistance management strategy had fallen apart. The EPA released a report on the failure in December 1996, promising revised management plans for 1997. The EPA had already acknowledged the complexity of resistance management strategies by limiting and/or prohibiting the planting of Bt maize where maize and cotton were grown in close proximity. The cotton bollworm is actually the same insect as the maize earworm. The EPA was recognising that non Bt maize could provide a refuge for cotton bollworm confronted with Bt cotton. The opposite strategy, of prohibiting Bt cotton where Bt maize was being grown, could also be used. If both the maize and the cotton were Bt crops, there would be a greater danger of insect resistance developing.

The economic and political implications are interesting. The farmer with the non Bt crop is actually providing a free refuge for the farmer planting the Bt crop, and might also suffer greater pest infestations than would otherwise be the case.

The EPA asked four questions:
1. What are the implications of the bollworm control failure for resistance management plans?
2. Should resistance management plans be mandatory or voluntary?
3. What scientific data are needed to evaluate the resistance plans?
4. Is Bt a public good?

The debate was acrimonious. The industry sought to describe the failure as a "learning experience". Frank Carter of the National Cotton Council said that "We disagree with the idea of failure of Bt cotton. Eventually these Bt survivors will be removed from the insect population." He did not explain how this was to be done. According to D.Hardee of Holdens Foundation Seeds, "The seed industry can conduct voluntary resistance management plans quite well on their own...Traditionally in the seed industry there has been no regulatory mechanism. We urge EPA to let us manage pesticide resistance ourselves."

Tom Carrato of Monsanto stated that "Monsanto believes the real issue is effective product stewardship and this must be a collaborative stakeholder process. Monsanto has established voluntary 'best available management practices' or BAMPS as we like to call them. These include binding growers to follow insect resistance management plans, mitigation plans and reporting any resistance management problems. It is the sincere vision of our company that sustainability represents the greatest good to the public.The EPA should not create a concept of public good." The public interest groups present at the hearing wanted all Bt crops to be suspended until a workable resistance management plan could be agreed. According to the Consumers Union, "Bt is a public good that should not be squandered. Bt toxins and the genes for insect susceptibility to those toxins are natural entities that make sustainable food and fibre production possible, are public goods whose fate should be determined by a broad range of stakeholders."

Margaret Mellon of the Union of Concerned Scientists asked the companies: "If you advocate voluntary efforts, are you willing to take legal responsibility for the success of these strategies? What about the loss of Bt efficacy? If you are really advocating responsible stewardship, you might set up a fund to compensate farmers once they lose Bt to resistance."(Pesticide & Toxic Chemical News March 26, 1997 pp17-19)

The failure of Bollgard turned out to be a failure in honest marketing and truthful labelling. Monsanto’s trials with the Bt cotton had shown quite clearly that it was lethal to the tobacco budworm and the pink bollworm but left the cotton bollworm relatively unharmed. However, this did not stop the company from misleadingly marketing its cotton as ‘Bollguard’.

3.3 THE ROLE OF THE ENVIRONMENTAL PROTECTION AGENCY

The EPA has played an essentially political role of trying to find a road through the conflicts surrounding Bt and Bt crops. The conflict is between individuals and organisations concerned about the environment, and individuals and organisations which stand to gain economically from the innovations. It is a conflict between economic and ecological goals.

The Editorial of Resistant Pest Management Vol 7 No 1 (1995) was devoted to an analysis of the role of the Environment Protection Agency in the management of insect resistance. It argues that "the EPA has a profound (and not altogether beneficial) impact on resistant management by virtue of its current regulations and could significantly improve resistance management with the adoption of additional or alternative policies. The merits of these proposals have been debated at length at various meetings, including by a committee of the National Academy of Sciences in 1986, and at various meetings of professional societies, iincluding the Entomolological Society of America. Recently, various public interest groups have added their voices to the chorus, urging that the EPA refuse to approve Bt-transgenic insecticidal crops untilthe EPA has in place workable, enforeable resistance management strategies."

"It seems clear that the EPA is reluctant to use regulation to help delay resistance to pesticides. In the EPA's defence, it may not have to do so. EPA has made some modest proactive efforts in avoiding resistance, such as requesting resistance management statements from some companies developing transgenic plants and more traditional pesticides. Nonetheless, in the absence of any efforts to enforce or facilitate the adoption of resistanc e management plans, such documents clearly have little more than public relations or educational value." (Roush.R. Dept of Entomology, Cornell University)

It is not possible to understand the policies of the EPA on Bt without considering the political environment within which these policies have been developed. What follows is an elucidation of the political environment and a consideration of the 1998 EPA White Paper on resistance management with Bt crops. We start with a consideration of the political role of key scientific societies.

3.3.1 THE POLITICAL ROLE OF SCIENTIFIC SOCIETIES

In July 1996 a coalition of eleven scientific societies sent a report to the EPA urging the Agency not to insist on mandatory controls over Bt crops. The eleven societies accused the EPA of "wanting to expand its federal regulatory powers," of "coining a new term," of discouraging "the development of new pest-resistant crops," of "prolonging the reliance solely on synthetic chemical pesticides," of eroding "public confidence in the safety of the food supply by sending the message that all plants contain pesticides."

A further two accusations actually had some basis. The societies argued that the costs of increased regulation would limit the field to a few large companies that could afford the development costs, thus denying the technology to small companies and public plant breeding programmes.

The societies stated quite correctly that the FDA and the USDA regulate the food and environmental safety of plants according to the risks posed by particular plants. They argued that the EPA proposed to categorise plants according to the method by which they were produced (genetic engineering) and by implication, they argued that this was not scientific, but arbitrary. There was a step missing in this argument. The EPA argued that the method by which the Bt plant was produced clearly raised new scientific issues in that no such plant had existed before, the mode of action of the Bt in the plant was unknown and the consequences for the environment of a plant that expressed a new poison throughout its growing life were equally unknown. The societies also argued that there

was no essential difference between plants that had been engineered to contain pesticides and plants which had always contained natural pesticides. This is an argument that cannot possibly be sustained in the light of the scientific publications on Bt that had been published by July 1996. It also needs to be pointed out that the two arguments are contradictory, though they do both lead to the same political position - which is to support the industry that now funds a considerable portion of their research in avoiding any regulation of the environmental and health questions concerning Bt plants. This intervention is mentioned here in order to indicate the sort of pressure that EPA officials are under and the ways in which so-called science is used for purely political objectives. The 11 societies were:
American Institute of Biological Sciences,
American Phytopathological Society,
American Society for Horticultural Science,
American Society for Microbiology,
American Society of Agronomy,
American Society of Plant Physiologists,
Crop Science Society of America,
Entomological Society of America,
Institute of Food Technologists,
Society of Nematologists
Weed Science Society of America.

The press release issued at the time reads as follows:
"WASHINGTON (July 31, 1996) Pending federal regulations threaten to stifle the development of alternatives to chemical pesticides, and 11 scientific societies today urged the Environmental Protection Agency to reconsider its policy before it becomes final. The EPA currently regulates chemical pesticides that are externally applied to plants. Now the agency wants to expand its federal regulatory powers over the characteristics of plants that help plants resist diseases and pests. The agency has coined a new term for these characteristics, calling them "plant-pesticides."

"This policy, if adopted, will discourage the development of new pest-resistant crops, thereby prolonging the reliance solely on synthetic chemical pesticides," said Calvin O. Qualset Ph.D., head of the Genetic Resources Conservation Program at the University of California, and a spokesperson for the 11 societies. "Furthermore, it will erode public confidence in the safety of the food supply by sending the message that all plants contain pesticides."

Eleven scientific societies, representing more than 80,000 members who study plants, food, plant pests and diseases, and plant defense mechanisms, developed a 35-page report detailing their scientific concerns with the proposal and suggesting principles for appropriate oversight. The report was sent today to EPA Administrator Carol M.Browner.

The report, "Appropriate Oversight for Plants with Inherited Traits for Resistance to Pests," emphasizes that all plants are able to prevent, destroy, repel or mitigate pests or diseases. That ability occurs naturally, and some crops have been bred for resistance to specific pests. EPA proposes to single out for regulation those pest-resistant qualities that were transferred to the plant through recombinant DNA technology (genetic engineering).

"This proposal threatens to limit the use of a cutting-edge technology to those developers who can afford to pay the increased costs associated with additional regulation and deny the benefits of the technology to small companies and public plant breeding programs," Qualset said.
"Food and environmental safety of plants developed through rDNA methods is already well regulated by the Food and Drug Administration and U.S. Department of Agriculture, he added. FDA bases its regulations on the principle of risk posed by a particular plant, not on the method by which the plant was produced. The societies argue that EPA's oversight of pesticides should be based on the same scientific principles underlying FDA's regulations."

3.3.2 UCS RECOMMENDATIONS FOR RESISTANCE MANAGEMENT

In 1997 the Union of Concerned Scientists convened a panel of six entomologists to survey the evidence and produce an independent report recommending management resistance options to the EPA. The entomologists were:

David Andow, University of Minnesota
David Ferro, University of Massachusetts
Fred Gould, North Carolina State University
William Hutchinson, University of Minnesota
Bruce Tabashnik, University of Arizona
Mark Whalon, Michigan State University

Fred Gould, William Hutchinson and Mark Whalon were also members of the Scientific Advisory Panel convened by the EPA in February 1998 to discuss Bt Plant Resistance Management. Their major recommendation for the management of resistance in Bt potatoes, maize and cotton are summarised below.

3.3.2.1 Bt Potatoes

1. The EPA should require a mandatory resistance management plan for Bt potatoes.
2. There should be a 20% refuge of non-Bt potatoes either in strips through the field or as a single block at the end of the field, or within 500 metres of the Bt potato field.
3. Imidacloprid should not be used in furrows or on leaves in the refuge
4. Refugia should be managed under IPM principles and pesticides should not be used until insect densities reach economically decisive thresholds.
5. A different crop should be rotated at least every third year.
6. Baseline insect susceptibility data should be developed for late instar larvae.
7. Monitoring programmes should be able to detect early and late instar larvae.
8. A substantial reward (perhaps $5000) should be offered to growers for discovering Bt resistant CPB
9. Monsanto should have a local eradication plan that provides step by step directions for collecting, shipping and eradicating Bt resistant beetles.

3.3.2.2 Maize

1. Mandatory resistance management plans are necessary for Bt maize and separate plans may be needed for each Bt maize hybrid on the market.
2. There should be a 50% treated or 25% untreated refuge of non Bt maize.
3. No Bt products should be used on treated refugia.

4. Refugia shouldbe adjacent or within Bt maize fields and there should be a refuge for every 320 acres of Bt maize

3.3.2.3 Cotton

1. Separate mandatory resistance management plans should be required, one for areas with pink bollworm, one for areas where this pest does not exist.
2. There should be a 50% treated or 16% untreated refuge of non Bt cotton.
3. Non Bt cotton should be planted close enough to Bt cotton to encourage mating between moths emerging from Bt and non Bt cotton, and where the pink bollworm exists, the distance should be reduced to take into account the limited mobility of the moth.

3.3.3 EPA WHITE PAPER ON Bt PLANT PESTICIDE RESISTANCE MANAGEMENT

Published on 14th January 1998, the stated purpose of the White Paper was as follows:
- "analyse data generated in the 1996 growing season for current resistance management plans for Bt plant-pesticides for Bt potato, Bt maize and Bt cotton,
- identify technical modifications that might improve approaches to resistance management
- identify areas of ongoing research and determine what might be required in the future for successful implementation of long term (sustainable) resistance management for Bt plant-pesticides in these and other crops." (p.1)

The Table below lists the pests that have been targetted by Bt crops in commercial production in the USA. The theory, economics and politics of resistance mnagement with Bt potatoes is relatively straightforward. The Bt potatoes are produced by one company (Monsanto) which has a monopoly of the market, and the potatoes are poisonous to Colorado Beetles, which will eventually become resistant. With maize things are rather more complicated because there are five economically important insect pests that eat maize in the USA and three companies competing for the Bt maize market with five different BT maize hybrids, each of which acts in a different way on the five pests. Bt maize is poisonous to the European Corn Borer. Its effects on the other maize pests has been the subject of field research which is summarised below. Cotton plants are eaten by three economically important insect pests in the USA. Bt cotton is produced by Monsanto, which has a monopoly of the market, and the plants are poisonous to the Tobacco Budworm. There has been considerable confusion as to its effects on the Cotton bollworm and the Pink Bollworm and this is discussed below. The situation is further complicated by Helicoverpa zea, which eats both maize and cotton plants with equal zeal. The common names of H. zea has resulted in further confusion. When it eats maize it is called the Corn Ear Worm and when it eats cotton it is called the Cotton Bollworm.

Table Insect Targets

Scientific Name	**Common Name**	**Acronym**	**Crop**
Leptinotarsa decemlineata	Colorado Beetle	CPB	potato
Ostrinia nubilalis	European Corn Borer	ECB	maize
Spodoptera frugiperda	Fall Armyworm	FAW	maize
Diatraea crambidoides	Southern Corn Stalk Borer	SCSB	maize
Diatraea grandissella	Southwestern Corn Borer	SWCB	maize
Helicoverpa zea	Corn Ear Worm	CEW	maize
" "	Cotton Bollworm	CBW	cotton

Pectinophora gossypiella	Pink Bollworm	PBW	cotton
Heliothis virescens	Tobacco Budworm	TBW	cotton

The EPA sought to review the evidence from the field on seven Bt crops produced by three companies. The Bt potato produced by Monsanto contains the protein toxin called Cry3A and has no competitors.

There are five varieties of Bt maize on the US market. Novartis has produced two varieties which both contain Cry1A(b) protein. Monsanto has also produced two Bt maize varieties with the same Cry1A(b) protein. DeKalb has produced a Bt maize containing the Cry1A(c) protein. The situation is then complicated by the fact that Monsanto's Bt cotton also contains the Cry1A(c) protein.

Table Bt Plants

Crop	**Primary pest target Company**	**Common Name**	**Bt toxin**	**Plant**
potato	L decemlineata Monsanto	Colorado Beetle	Cry3A	Newleaf
maize	Ostrinia nubilalis Novartis	European Corn Borer	Cry1A(b)	Bt176
maize	Ostrinia nubilalis Novartis	European Corn Borer	Cry1A(b)	Bt11
maize	Ostrinia nubilalis Monsanto	European Corn Borer	Cry1A(b)	MON801
maize	Ostrinia nubilalis Monsanto	European Corn Borer	Cry1A(b)	MON810
maize	Ostrinia nubilalis DeKalb	European Corn Borer	Cry1A(c)	DBt418
cotton	Heliothis virescens Monsanto	Tobacco budworm	Cry1A(c)	Bollgard
cotton	Helicoverpa zea Monsanto	Cotton Bollworm	Cry1A(c)	Bollgarg
cotton	P. gossypiella Monsanto	Pink Bollworm	Cry1A(c)	Bollgard

Table. Commercially Available Bt Maize in the USA

trade name	**Knockout** **Natureguard**	**Bt-Xtra**	**Yieldguard**
engineer	Novartis	DeKalb	Monsanto/Novartis
seller	Novartis/Mycogen	DeKalb	Pioneer, Cargill DeKalb, Golden
Bt toxin	Cry1Ab	Cry1Ac	Cry1Ab
Tissue	green tissue pollen	leaf, kernel stalk	leaf,pollen tassel, silk

	stalk	silk	kernel
Level	early season high late season low	full season high in leaves lower rest	full season high all parts

In theory the White Paper presents an open agenda but in practice most attention is concentrated on the resistance management paradigm that has already been selected by the genetic engineering industry. The EPA started issuing registrations for Bt plants in 1995 and the first growing season was 1996. Refuge requirements were made mandatory for Bt cotton but not for the Bt maize or Bt potatoes. The EPA, having accepted the preferred industry approach to resistance management, then mandated specific resistance management data requirements and mitigation measures for all the Bt maize and Bt cotton licenses. The licences for Bt maize are time-limited to five years and are due to expire on 1/4/2001; those for Bt cotton expire on 1/1/2001. Renewal of the registrations was to be conditional on the successful completion of research on resistance management. There is no time limit on the Bt potato licence.

The companies were charged with the collection of various data:
- target pest biology and behaviour
- secondary pest biology and behavious
- population dynamics of the pests
- cross-resistance potential
- refuge strategies
- dose deployment adequacy
- discriminating concentrations of toxins
- monitoring methods
- reporting methods for resistance

The same conditions were not applied to the Bt potatoes because the EPA deemed that the agreement between Monsanto/Naturemark and each of the Bt potato growers met their required conditions for the deployment of a refuge strategy and reporting of insect resistance.

The EPA has thus placed the burden of proof fairly and squarely on the genetic engineering industry. The industry has to prove that Bt crops are environmentally safe. Unfortunately, this results in a disproportionate number of entomologists working on research contracts within the narrow confines of the company paradigm - a high dose/refuge strategy. It also means that much of the research remains confidential for reasons of commercial competivity until it is formally required by the EPA. The question as to whether the company paradigm provides the best strategy, or whether a combination of strategies within an IPM approach will produce better results has now been side-lined.

Whilst continuing to mention the need for multiple tactics, the EPA immediately narrowed the problem to high dose/refuge questions:
"Good resistance management is dependent on multiple tactics to decrease the selection pressure on the target pests and employment of different mortality sources. For Bt plant-pesticides, as for conventional pesticides, an overall IPM programme should include pest resistance management. The characteristics of plant-pesticides allow the implementation of unique pest management strategies. An example for Bt plant-pesticides is the use of a high dose expression strategy coupled to the use of an effective refuge as important resistance management tools." (p.2)

The industry has focussed in on one key aspect of resistance management plans. More time and effort has been spent arguing whether RMPs should be legally binding than on what RMPs are the most appropriate. The EPA has implicitly - and possibly unintentionally - indicated that this is an issue that the industry can fight for by oscillating between mandatory and voluntary approaches to RMPs. When the EPA decided not to make registration of the Bt potato conditional upon a mandatory RMP, it was in effect rewarding Monsanto for "good practice". The "good practice" consisted in recommending a refuge to farmers planting Bt potatoes in 1996. One year later, after public interest groups had criticised the lax controls, Monsanto made 20% refuges a mandatory part of their contracts with growers.

When the EPA made the registration of the Bt cotton and Bt maize conditional on certain mandatory requirements, it was in effect criticising the industry for not having done enough. The lesson that has been learned by the industry is that it is better to offer the EPA slightly more than they have done so to date if by doing so they can avoid mandatory controls. This comes out clearly in the industry comments to the SAP Hearings on 9-10/2/98, where reference is constantly made to the concept of "responsible product stewardship".

The industry has indicated "that EPA should not establish 'additional hurdles' to the development and implementation of these new Bt plant-pesticides and that it is industys (including seed company's) responsibility to ensure the successful development and implementation of resistance management strategies. That is, resistance management to Bt plant pesticides should be handled on a voluntary basis........Market forces should dictate resistance management strategies. EPA's role should not be one of enforcement of resistance management plans." (p.6)

"Some individuals from industry and academia/USDA indicated that EPA shoould not single out Bt plant-pesticides for resistance management requirements. As the statemenet from Pioneer Hibred International notes, 'EPA must be equitable in imposing data requirements: it should not single out plant-oesticides for requirements that have not been, and are not beeing imposed on numerous other registrants of Bt pesticides.' Other individuals noted that the agency did not impose resistance management requirements on conventional chemicals that posed a high degree of selection pressure for ressistance on the same target insects as Bt plant-pesticides, e.g. imidacloprid, spinosad, fipronil and ninsect growth regulators. Pioneer Hibred International suggested that if a mandatory role was necessary for implementation of ressistance management strategies it should be USDA rather than EPA that should have the lead." (p.7)

Mark Whalon, entomologist from the University of Michigan, gave a short answer to the industry position:
"First, the EPA should require resistance management plans for all newly registered conventional or biological pesticides which will be sold into markets where target or non-target insects, mites, nematodes or pathogens have developed resistance in the past."
"Second, the Agency should be required to have independent scrutiny of the enforcement of the susceptibility management (refuge0 in the case of cotton and maize Bt-transgenic plants."
"Third, EPA sgould convene a Science Advisory Panel to advise the Agency of the development of a compreehensive susceptibility management assessment process in the Agency's pesticide registration responsibility." (p.5)

The ad-hoc, and post hoc factum status of EPA policies, amounting in the eyes of various public interest groups to culpable irresponsibility, is made clear by the Agency itself. In

1995 the EPA permitted the field cultivation of Bt crops. With regard to bt potatoes, the "EPA did not require as part of the registration more information on the biology on Colorado potato beetle resistance and the potential for cross-resistance." (p.16) Only much later did the EPA start seeking "comment on the scientific information needed to develop effective resistance management plans. That is, what kinds of data are necessary to assess the potential for pest resistance and/or adequately evaluate proposed resistance management plans." (p.8)

The EPA again sought evidence on whether Bt is a "public good". Committed as it is to patenting genes in the name of private intellectual property rights, the industry was uniformly opposed to the use of such concepts. The entomologist, Mark Whalon, stated that "susceptibility genes in pests are natural resources which are in the public good and should be protected. He comments that the loss of susceptibility genes through the overuse of pesticides constitutes a tragedy of the commons no less significant than polluted air, watwer or contaminated food. All mankind suffers from the consequen ces of this genetic over-exploitation which can be and should be prevented." (p.11) The Union of Concerned Scientists indicated that "Bt is a public good that should not be squandered".

3.3.3.1 Bt potatoes

The BtCry3a Potato was the first ever plant -pesticide to be registered in 1995. In 1996 the Bt potatoes accounted for 1% of the US crop. In 1997 this had increased to 2.5% of the total. Three varieties of potato have been developed as Bt plants by Monsanto - Russet Burbank, Superior and Atlantic. in principle it is possible to engineer Bt genes into any variety of potato. All research to date suggests that the Bt potatoes produce a consistently high expression of the toxin throughout the season. Experiments with mixtures of Bt and non-Bt potatoes indicated that insects moving between plants could survive for a while on Bt potatoes, thus increasing the risk of resistance appearing within the population. The EPA did not require a refuge when Bt potatoes were registered in 1995. In 1996 Monsanto simply recommended that farmers planted a 20% refuge. In 1997 Monsanto required farmers to sign a contract in which they had to plant a 20% refuge, with detailed recommendations for spatial arrangements and cultivation practices. The refuges could be treated against CPB, but only with foliar non-Bt insecticides and not with systemic insecticides so that some beetles survived. The recommendation includes killing the Bt potato vines first so that any Bt-resistant beetles migrate to the non-Bt crop and mate with susceptible insects. Monsanto has stated that it intends monitoring contract compliance.

Between 1992 and 1996, Monsanto analysed the susceptibility of 79 different populations of CPB from Canada and the USA.. There was a seven-fold difference in susceptibility to Cry3A. Trials with CPB resistant to Bt sprays showed that a diet of Bt potatoes sufficient to kill 100% of susceptible populations killed only 26% of these beetles.

The EPA received only 4 comments specifically on Bt potatoes from the public hearings in 1995 and 1996. An integrated biological cybernetics company criticised the Monsanto plans on the grounds that they could harm beneficial insect populations. The EPA considers this argument to be rebutted by the evidence that beneficial arthropod populations were higher in Bt potato fields than in potato fields treated with chemical pesticides (though not high enough to control late-season aphid control). However, no serious conclusions can be drawn from such evidence, given that this was the first time Bt potatoes had been grown. More recent research considered in Chapter 2 indicates that beneficial insects that feed on Bt-plant eating insects are indeed harmed.

Many commentators now expect CPB resistance to Bt potatoes to take some time, but not because it is not inevitable or because Monsanto's resistance management plan works. The reason, ironically, is that a new chemical pesticide for use against the CPB out-performs the Bt potatoes and no refuge is required. Rapid farmer acceptance and use of imidacloprid has somewhat eclipsed Bt. According to Mark Whalon, entomologist, there should be a refuge requirement for imidacloprid.

3.3.3.2 Bt maize

The EPA has registered five Bt maize varieties, four of which express Bt Cry1A(b) and one of which expresses Bt Cry1A(c). According to the EPA "understanding these (plants) and how they affect performance is crucial to the wise selection of corn hybrids and to appropriate resistance management".(p.21) Each of the five Bt maize varieties have been given conditional registrations which will be converted to unconditional registrations after 1/4/2001 if the applicant's resistance management plan is considered to be effective. Because of questions that arose at the time of registration, the EPA required, as part of the registration, the development of a monitoring programme including surveillance and remediation, grower education, and the maintenance of a confidential sales database. Each registrant was required to sunmit annual progress reports on research results and conclusions in the following areas:

1. information on ECB pest biology and behaviour
2. feasibility of refuge options
3. development of discrimination dose concentration assay
4. effect of Cry1A(b) or Cry1A(c) toxins on pests other than ECB including the CEW/CBW
5. the biology of ECB resistance and cross-resistance

The EPA also required the companies to submit annual sales data for each state. because the detailed information is considered to be commercially sensistive, only the gross statistics are available in the public domain. In 1996 about 400,000 acres of Bt maize were planted in 30 states, amounting to about 0.5% of the total. In 1997 the acreage increased to between 3,500,000 and 4,000,000 acres, amounting approximately 5% of the total.

The EPA recognised that the development of CEW/CBW resistance was a major concern but did not require studies of the problem. (p.22) Although no specific refuge strategies were mandated at the time of registration, the registrants "were required to collect research data regarding different refuge srategies in order to determine the necessary arrangement and relative size of Bt and refuge plots for a long-term resistance management plan." (p.22) Seed mixes were eliminated as an effective refuge strategy because of relatively high ECB larval movement.

Monsanto and DeKalb made 5% unsprayed or 20% sprayed refuges mandatory in their conttracts with growers for the 1997 season. Novartis merely recommended the use of a refuge.

Because of concern over the effects of Cry1A(b) and Cry1A(c) maize on CEW in southern areas where Cry1A(c) cotton was being grown, the EPA decided to impose restrictions in the southern USA on the number of acres of Bt maize expressing the Bt toxin in the silks and kernels that could be planted.

This had the effect of restricting plantings of the Monsanto produced MON810 and the Novartis produced BT11 to 100,000 acres each. The DeKalb produced DBT418, which came later in the registration queue, was refused registration in parts of the south on the grounds that any extension of the area beyond 200,000 acres would rwesult in too high a resistance risk. However, the Novartis produced 176 Bt maize, which expresses only a trace of Bt in the silk and kernel, was not subject to these restrictions. The Texas Corn Growers Association, Novartis and the University of Missouri have argued that this restriction should be removed on the grounds that Bt maize is a more profitable crop than Bt cotton. (p.46)

In addition to these sales restrictions, the EPA also required research data and model development on the potential impact of Bt maize on Bt resistance management where both cotton and maize are grown in the same area.

According to the EPA:
"Silk and kernel expression in Bt maize hybrids will likely increase the selection for CEW resistance especially in cotton-growing areas. If there is silk expression of the Cry1A(b) or the Cry1A(c) delta endotoxin at sufficient levels to select for resistant CEW, then resistant CEW could move from Bt maize to cotton or Bt cotton, posing potentially significant problems in cotton or Bt cotton or potentially in other crops affected by CEW. Where maize and cotton acres are in close proximity, there will be migration of second generation CEW from silk stage Bt maize to cotton and Bt cotton and other crops. In the southeastern US, virtually all second generation CEW funnel through maize where they complete development on the ear of this preferred host. Selection for CEW/CBW resistance could be accelerated if Bt maize hybrids became widely adopted in the south if adequate resistance management was not adopted. in the south there are 3-6 CEW generations and in the north there are 1-2 generations. Thus CEW in the south are potentially subject to higher levels of exposure to the Bt delta endotoxin than CEW in the north. CEW only overwinter in the south. However, the development of CEW resistance to Bt in the north is also a concern. The major source of CEW in the northern corn belt is adults flying or being carried by prevailing winds from the southern states each year. Should CEW resistance to Bt toxins develop in the south, it could be equally damaging in the northern states growing Bt maize each season. In the south, there would be a higher selection pressure in areas in which Bt maize and Bt cotton are in close proximity, and in areas in which Bt microbial pesticide products are used. Resistant CEW could lead to failure of Bt microbial pesticides used on cotton and other crops or to the failure of Bt cotton and Bt maize, and other crops both in the south and in the north for control of CEW. Although the risk of loss of Bt and increased use of chemical insecticides cannot be quantified, EPA believes this risk is real." (pp23-24)

The EPA then considers the implications of several companies competing for the same Bt market. While the theory of high dose expression coupled to effective structured refugia is relatively straightforward, its implementation and enforcement remain controversial. Long-term Bt maize resistance management is complicated by the following circumstances:
1. There are several companies competing for the technology
2. The companies are using different Bt delta endotoxins in Bt maize
3. Each Bt maize has different levels of Bt expression in various parts of the maize plant
4. Because the companies are in competition their research efforts are not consolidated
5. Bt maize is grown across many states, involving a large number of farmers.

"With all these factors in mind, there is disagreement among stakeholders as to what is:
1. the appropriate arrangement and relative size of Bt maize and refuge plots
2. the nature and objective of performance-monitoring activities

3. research co-ordination
4. appropriate incentives to foster grower education and acceptance." (p.24)

In June 1995 the entomologist Richard Roush from Cornell University opposed the unrestricted registration of the Novartis Bt maize 176 on the grounds that "transgenic maize will be controlled by perhaps 5-6 companies in an already intensively competitive seed market, increasing the chance that competition for market share will derail any voluntary resistance management effforst that involve using non-transgenic refuges......Along with other university faculty, I have proposed to Novartis and your agency (EPA) how this issue can be quickly resolved.......EPA should simply require that the companies promulgate a workable plan to ensure that at least 20-50% of the maize on any given farm is not transgenic." (letter to EPA 23/6/95) Neither the EPA nor Novartis heeded the advice.
"

Resistance Management Strategies

1. Does Bt maize produce a high dose of toxin?

The primary target of Bt maize is ECB. According to the EPA, "all the registered Cry toxins in maize express a dose sufficiently high to control first-generation ECB in whorl stage maize. However, the level of control against late season ECB generations differs between Bt plant pesticides.......Measured in terms of reduction in tunneling damage, the level of control for BT11 (Novartis), MON810 (Monsanto) and DBT418 (DeKalb) derived hybrids is greater than 95% for first generation ECB whereas the level of control for 176 (Novartis) hybrids is greater than 95% for first generation ECB and about 70-75% for decond generation ECB....Because some hatching larvae initially colonise ears to feed on silks and developing kernels, these larvae survive on 176 and may tunnel later in stalks and ear shanks. The presence of second generation ECB in ears of 176 maize is a topic of resistance management discussions." (p.25) The entomologist Fred Gould concluded that "176 line of Bt maize does not produce a high enough dose to be considered as part of a resistance management programme for ECB that requires a high dose in the plant during the period when second generation larvae are present". (p.26)

Four other maize pests are partially susceptible to the Cry1A(b) and Cry1A(c) toxins -

- the southwestern corn borer	(SWCB)
- the fall army worm	(FAW)
- the southern cornstalk borer	(SCSB)
- corn ear worm/cotton bollworm	(CEW/CBW)

Because the use of these Bt crops can induce selection for resistance in these insects, the EPA has asked for data regarding the possibility of resistance in these secondary pests, plus plans for managing such resistance as a condition of registration of the Bt lines.

Potential confusion amongst farmers arises from the fact that some companies make no control claims for these pests, whilst others do. Either way there is a problem. If the Bt maize is partially effective but the farmer does not know, then the potential for insect resistance is increased. If, on the other hand, the company claims that the Bt maize is effective when this is only partially so, the farmer is being misled.

Novartis has made no claims regarding line 176. However, laboratory research showed that the FAW and CEW were poisoned by the Bt 176 maize. This evidence was replicated by field trials, where CEW caused damage to Bt maize at the whorl stage. However Bt maize 176 was 20-50% effective on SWCB and 65% effective on SCSB. The other Novartis maize - BT11 - provided full season control of the SWCB, as did the Monsanto MON810 maize.

Monsanto claimed that MON810 controlled the SWCB and was required to submit available research on possible resistance development in CEW. Only a third of the CEW larvae developed successfully on MON810. Fred Gould, entomologist, concluded that MON810 could change the phenology of adult CEW moth flights from maize to cotton leading to a need for alteration of scouting procedures for resistance in cotton. (p.28) Further field research indicated that CEW development in late-planted maize was delayed on MON810, and BT11 hybrids, and less delayed on 176 maize hybrids. Other studies showed that the weight of larvae eating BT11 and MON810 maize was 82-90% below normal whilst on 176 maize there was only a 41-64% reduction.

DeKalb made no claims that DBT418 controlled or suppressed CEW. Field studies indicated that larvae feeding on DBT418 had slightly reduced weights.

The EPA required Monsanto and Novartis "to submit available research data on CEW relative to resistance development and plans for producing resistance predictive models to cover regional management zones in the cotton belt based on CEW/CBW biology and cotton, maize, soybeans and other host plants". (p.31) The following Table summarises the research currently in the pipeline.

Table Impact of Bt Maize on Bt Insect Resistance Management in Cotton

Research	**University**	**Funding**
1. computer simulations	N Carolina State	Monsanto, DeKalb
2. CEW and 176	Mississippi State	Novartis, Mycogen
3. CEW population dynamics	Mississippi State	
4. Long migration of adult EC	Minnesota	Novartis, Mycogen
5. Short migration of adult ECB	Nebraska	Novartis,Mycogen, DeKalb,Monsanto
6. movement of ECB into Bt maize	Iowa State	DeKalb,Monsanto,Novartis
7. ECB lifetable	Illinois	DeKalb, Monsanto
8. Overwintering survival of ECB	Nebraska	Novartis, Mycogen
9. Effect of Cry1A(c) on ECB fitness	Minnesota	Novartis, Mycogen
10.Cross-resistance	Minnesota	Novartis, Mycogen
11.laboratory selection of resistance	Delaware	Novartis
12. Midgut binding studies	Minnesota	Mycogen

2. What is an effective refuge?

Whilst there is general agreement that a refuge is a necessary, there is no concensus concerning the size or deployment of refugia. When the first Bt maize was registered in 1995, the EPA "thought that based on market penetration estimates there would be enough non-Bt crop acreage to serve as a viable refuge in the first five years following full-scale commercialisation." (p.36) "In 1996 and 1997 less than 5% of the total maize acreage was planted with Bt maize hybrids and of this acreage, the density in any county or state was low."(p.37) In other words, as luck would have it, the market managed to provide an adequate refuge strategy.

In April 1996 the USDA convened a forum on Bt Resistance Management. At the same time the NC-205 Consortium started work on resistance management. A consensus emerged regarding a treatable refuge of 20-30% of the total maize sown. "In continuous maize acreage sprayed with insecticides, the refuge size would be increased to perhaps 40% to compensate for larval mortality." (p.37)

Whilst Monsanto and DeKalb both mandate structured refugia in their contracts with farmers, Novartis merely indicated its commitment to the "development of long-term resistance management strategies through the support of research efforts" and through 1996 and 1997 they neither mandated nor even recommended a particular refuge option. Late in 1997 Novartis announced that they would recommend the NC-205 guidelines to farmers for the 1998 season but they remained unwilling to make refugia a contractual obligation.

The following Table summarises the research currently in the pipeline.

Table Research on Size and Deployment of Refugia

Research	**University**	**Funding**
1. structured planting timetable	Iowa State	Novartis, Mycogen
2. halo effect of Bt maize	Minnesota	Novartis,Mycogen, DeKalb,Monsanto
3. survival of ECB on non-maize	Iowa State	Novartis,Mycogen, DeKalb,Monsanto
4. sequential plantings	Pennsylvania State	DeKalb, Monsanto, Novartis
5. optimisation model	Iowa State	DeKalb, Monsanto
6. strategy evaluation	Kansas State	DeKalb,Monsanto, Novartis
7. BT11 &MON810 impact on ECB	Delaware/Michigan St	DeKalb, Novartis
8. grower attitudes to refugia	Nebraska/Iowa St	Novartis, Mycogen
9. Bt maize impact on CEW	Maryland/Virginia St	DeKalb, Monsanto
10.baseline data for monitoring	Nebraska	Mycogen,Novartis, Monsanto,DeKalb
11.CEW baseline susceptibility	USDA/ARS	DeKalb, Monsanto

It is not known what percentage of US entomologists specialised in the target insects are now working on contracts within the high dose/refugia resistance management strategy for Bt crops, or what percentage of the research funds dedicated to the study of these insects is now being spent on these strategies rather than on the bigger issues concerning the sustainable use of biopesticides. Everyone agrees that resistance management strategies can only delay the onset of insect resistance. It is an esssentially futile intellectual effort.

3.3.3.3 Bt Cotton

In 1995 the EPA registered the Bollgard Cotton produced by Monsanto containing the Cry1A(c) toxin.
this remains the only Bt cotton on the US market. According to the EPA, "there are two primary resistance concerns for the registered Bt cotton:
1. development of resistance in the primary target pests TBW, CBW and PBW
2. cross-resistance to the Cry1A(c) and other Cry delta endotoxins expressed in other Bt plant pesticides or Bt microbial products. The Agency concluded that to manage

resistance in the long term and to develop a long term resistance management strategy, specific data needed to be collected on all three target pests and required such data to be generated. A multi-factor resistance management plan was required to be implemented as a condition of the registration for Cry1A(c) cotton. The Bt cotton registration required a structured refuge and included grower education and training." (p.50) All the EPA requirements were made that much easier by the fact that there was only one company in the market.

Two specific refuge options were mandated as requirements of registration:
- either a 20% refuge that could be treated with insecticides other than Btk
- or a 3.8% refuge that could not be treated with acephate, amitraz, endosulfan, methomyl, profenofos, sulprofos, synthetic pyrethroids or Btk

Where the Bt cotton acounted for more than 75% of the total cotton planted in a single county or parish, growers using the 3.8% refuge option were obliged to plant the refuge within a mile of the Bt cotton.

The EPA required Monsanto to submit annual sales figures as a condition of registration. Two varieties were sold in 1996 - NuCotn33 and NuCotn35. About 6000 growers planted 1.8 million acres, representing about 14% of the total US crop. In twenty two counties across Florida, Alabama, Georgia, Louisiana, Mississippi, North Carolina and Texas the Bt cotton exceeded 75% of the total planted.

Nine Bt cotton varieties were sold in 1997 and the Bt cotton acreage increased to about 2.3 million acres. All researchers and commentators agree that the Bt cotton expresses a high dose of the toxin and is currently lethal to TBW. However, the toxin only kills between 80% and 95% of CBW, which is also an important pest. In other words, the Bt cotton expresses a low dose of the toxin for CBW. In 1996 the CBW populations were the highest in 10 years in the south east of the cotton belt. The fact that this outbreak was only partially controlled by the Bt cotton, plus the misleading impression given by Monsanto, who confused just about everyone except the entomologists by naming their cotton "Bollgard", produced panic amongst farmers. They were, justifiably enough, under the impression that Bt cotton was lethal to the CBW and therefore thought that the CBW must have become resistant to Bt. They then panicked into applying chemical insecticides as soon as they spotted some damage to the plants. One Monsanto brochure that was mailed to growers advised them to "Just relax. Bollgard will protect your cotton." and over a picture of a bollworm was the headline, " You'll see these in your cotton and that's OK. Dont spray."
Shares in Delta and Pineland, the Monsanto subsidiary that distributed the Bollgard Cotton seed, were briefly suspended on Wall Street and when trading resumed the share price was down by 22%.
Subsequent research showed that the CBW had not developed any new resistance to Bt but it was also clear that a considerable percentage of the CBW are naturally resistant toBt cotton. One of the main arguments in justification of the Bt cotton - that it eliminated the use of environmentally damaging chemical insecticides - turned out to be false. According to entomologist, Fred Gould, the CBW is likely to become generally resistant to Bt cotton much sooner than the TBW, simply because many insects exposed to the Bt cotton can survive. "If one assumes the initial frequency of a partially recessive resistance allele is 10 -3 for CBW.....then genetic models predict that CBW populations could become resistant to the Bt cotton in 3-4 years even with the 4% refuge currently in use." (p56)

According to the EPA, any long term resistance management strategy for cotton depends on an understanding of the biology and ecology of TBW, CBW and PBW. Unfortunately, "there is limited knowledge on the genetics and mechanisms of resistance to Cry1A(c) in TBW, CBW and PBW. Gould produced a laboratory population of very resistant TBW before the EPA even licensed Monsanto's its Bt cotton. In another laboratory experiment TBW resistant to Cry1A(c) were also resistant in varying degrees to Cry1A(a), Cry1A(b), Cry 1B and Cry1C.

The Bt cotton is not particularly poisonous to the CBW and Monsanto informed the EPA that this was the case at the time of registration. According to the EPA, "All the available evidence supports the conclusion that a structured refuge is necessary to the success of a long-term resistance management strategy. Two refuge options were mandated as requirements of the Bt cotton registration to mitigate the development of resistance: 20% sprayed refuge or 4% unsprayed refuge." (p.62)

Problems have emerged with the 4% refuge option because the TBW has so decimated the refuge that it is doubtful whether sufficient susceptible insects reach adulthood. Fred Gould "commented that Bt cotton does not provide a high dose strategy for control of CBW and PBW. Furthermore, the current refuge options associated with Bt cottton amounted to an efffective refuge size of 4% and in his estimation the effective refuge size would need to be increased to counterbalance the lack of a high dose for CBW. Gould indicated the effective refuge size for Bt cotton, under the current dose situation, would have to be at least 30% non-Bt cotton. A panel of Texas A&M entomologists stated in their written coments to EPA that a 30% unsprayed refuge may be impractical or too costly to the grower. They recommend that a 20% non-Bt cottton sprayed refuge be planted and managed in a manner to coincide with the Bt cotton so the refuge is attractive to oviositioning CBW adults and will produce moths at the same time and in the same geograpohical vicinity as the Bt cotton, i.e. within one mile of the Bt cotton. They recommend that the 4% unsprayed refuge should be replaced with a 20% sprayed refuge. They explained that a 20% sprayed refuge should be effective as long as the combined maize, sorghum and soybean acreage is planted in relatively close proximity to the Bt maize to act as a refuge, and is greater than the Bt cotton acreage in these Bt cotton producing counties." (pp.62-63)

According to entomologist Tabashnik, "the 4% unsprayed refuge may not produce enough susceptible insects throughout the growing season and the 20% sprayed refuge may suppress susceptible insects because of the effectiveness of the conventional pesticide treatments. In both cases, the refuges would be ineffective." (p.64)

Monsanto is wholly or partially funding a number of research projects to help determine what constitutes effective refuges for all three cotton pests. The EPA requires the company to have a workable resistance management strategy, a monitoring plan and a plan for remedial action as and when resistance appears. Monsanto was also required to develop educational material for growers on the resistance management in Bt cotton. In 1996, a Monsanto survey of 89 cotton growers showed "an average yield improvement of 5% to 16% depending on the cotton-growing region. Taking into account total insecticide system control costs and yield, they saw an economic advantage of $33 per acre from using Bt cotton even after paying the $32 technology fee. Planting of Bt cotton resulted in the elimination of the equivalent of a quarter million gallons (650,000 litres) of formulated insecticide products in the US." (p.69) Whilst there is no doubt that there can be immediate net benefits from planting Bt crops, all the evidence suggests that these benefits are temporary and that the longer term consequences are potentially worse than when the Bt crops were first planted.

3.3.4 SUMMARY

This, then is the essence of the science and the politics of Bt prior to the meeting of the Science Advisory Panel in Washington in February 1998. It can be seen that the lines had been clearly drawn and all the arguments had been well rehearsed.

3.4 EPA SCIENTIFIC ADVISORY PANEL ON Bt PLANT RESISTANCE MANAGEMENT Washington 9-10 February 1998

The panel of fourteen scientists included eleven entomologists, no economists and no ecologists. They were presented with a list of leading questions which made it impossible to discuss the wisdom or effectiveness of the paradigm within which the EPA was working. The two days were thus limited to a discussion of the details of a resistance management approach which was itself highly questionable.

3.4.1 THE QUESTIONS POSED

The EPA asked the panel to discuss 13 questions:

1. What further information is required on pest biology and their population dynamics?
2. What constitutes a high, moderate and low dose of a plant-pesticide toxin?
3. What secondary/minor pests are of concern for long term management of Bt crops?
4. Is there agreement regarding the mechanisms and genetics of resistance?
5. Is there agreement regarding the potential for cross-resistance?
6. How can predictive modelling be best used to devise long term management strategies?
7. Are there alternate modes of action that would not be effective?
8. Can/should Bt crops be integrated into IPM programmes?
9. Are refuges an essential part of long term management strategies?
10. Should target pests be routinely monitored for resistance?
11. Are the current remedial action plans for reports of resistance adequate?
12. Are refuges necessary for crops on limited areas (120,000 ha)?
13. What factors do farmers consider regarding refuge strategies?

Almost every time that one of the panelists tried to raise issues beyond the high dose/small refuge resistance management strategy they were ruled out of order and were silenced by the chairperson. On the few occasions when ecological or economic issues were allowed an airing (as in question 13, for instance, which is primarily a socio-economic issue), the panelists sought refuge in the limits of their competence because they were entomologists. Such considerations also prevented them from contributing to discussions that did not concern the particular insects they were studying.

For example, the EPA asked the following:
Question 5E:
"Does he subpanel agree with EPA's analysis that pyramiding two Bt genes with different modes of action is a powerful tool in managing resistance?"
The question raises several other questions:
1. Does an EPA statement of opinion make it easier or more difficult for a scientist to comment?
2. How come the EPA arrives at an opinion in advance of a scientific advisory panel meeting?

3. Why is the question posed in the form which requires a yes-no response when the only possible response must state that it depends on a host of other factors?

Question 9E:
"Does the subpanel have any scientific evidence that indicates that a 20% structure refuge is an inadequate refuge for CPB resistance management in the long-term?"
1. Why does the EPA use the term "inadequate" rather than "adequate"?
2. What implications does the EPA formulation of the question have for the precautionary principle?

Question 9F(3):
"Is there any scientific evidence that indicates whether a 5% unsprayed or 20% to 30% sprayed refuge is inadequate for long term resistance management?"
Official answer from the Chairperson:
"No"
Unofficial spontaneous answer from one of the panelists:
"There is no evidence that these refuges are adequate, either."

The answers to other questions were revealing:

Question 9F(5):
"Are variations in refuge size and structure appropriate for different regions of the country, especially northern and southern corn (maize) growing regions?"
Answer:
"Yes"

Question 9G(1):
"Is there any scientific evidence to indicate whether the 20% sprayed or 4% unsprayed refuge option is superior to the other?"
Answer:
"No"

3.4.2 COMMENTS FROM STAKEHOLDERS

The Panel received information from a number of organisations. The environmentalists, consumers and organic farmers raised a number of ecological and health issues. The agrochemical industry evidence to the panel concentrates on one issue - their wish to avoid mandatory resistance management strategies.

3.4.2.1 Greenpeace

"Even if the Agency and industry achieve the unlikely goal of establishing practical and effective RMps, we have no guarantee that trhese same RMPs will be observed and enforced by other nations where Bt crops are planted. Of particular concern are the plantings of Bt crops in Canada and mexico. A lack of adequate RMPs in these countries wouldlead to insect resistance, and since insect ppulations are not known to respect national bioundaries, American farmers would still eventually face the problem of bt resistant pests. This problem will be exacerbated by Mexico's status as a centre of origin for maize. With the outcrossing of Bt maize genes among wild and weedy relatives in Mexico and Central America, and the subsequent expression of the Bt toxin among these plants, RMPs become obsolete. In this situation the high dose/refuge model will fail to

apply, as native vegetation will no longer serve as an untreated non-Bt refuge for non-resistant insect populations. Because of Bt's importance to organic farming and IPM, Greenpeace views Bt as an important and irreplaceable public resource. Any loss or diminution of effectiveness due to the reckless approval process and lack of adequate oversight of transgenic Bt crops is unreasonable, unaccdeptable and an assault on the public good."
Paul Clarke, Greenpeace International

3.4.2.2 International Centre for Technology Assessment

"Transgenic Bt plant pesticides are one technology that will have an unreasonable adverse effect on our environment and economy. The widespread use of transgenic Bt plant pesticides will lead to the development of Bt multiple resistance in major pests within a relatively short space of time, will result in the transfer of bt traits to progenitor plants and wild relatives and will have harmful impacts on beneficial, non-target organisms..... As the agency seeks answers today to its select questions it is really admitting that it has not yet fully assessed the environmental and economic impacts of insect resistance to Bt even though it has already approved the transgenic crops that cause the resistance.......Such action is grossly negligent - the agency admits that resistance will happen, it continues to register the lant pesticides it knows causes the resistance, and then it admits it has no real idea what mandatory or enforceable resistance management plans will look like."
Joseph Mendelson, ICTA

3.4.2.3 Consumers Union

"The EPA has raised a number of intriguing technical questions regarding the possible efficacy of Bt resistance management plans based on the high dose plus refugia strategy. Whilst these questions warrant further research focus, they obscure what is really important about this two day meeting. EPA's conditional registration of bt-transgenic cotton an maize was based on the requirement that proven, effective RMPs be in place..........Once resistance genes emerge and gain a foothold in populations, they cannot be recalled.......The four key assumptions that underlie the RMPs for all transgenic crops released so far are:

1. High dose strategy is effective
2. Refugia are effective
3. Resistance is a rare, recessive trait that carries significant fitness costs
4. Resistance to different Bt toxins is independent

New evidence published in the last year fundamentally and irrevocably undermines these four assumptions. Furthermore, there is a consensus amongst most independent entomologists and experts in Bt resistance management that resistance is just a matter of time. Industry urges farmers not to worry because new technologies and biopesticides will be available as older ones lose effectiveness. They are, in effect, asking consumers and farmers to give up a sure-bet for a roll of the biotech dice. Public health officials said the same thing about human antibiotics 15 years ago and now we are down to one for some ailments."
Michael Hansen, Consumers Union

3.4.2.4 The Edmonds Institute

"Because of growing consumer concern about the use of non-biological pesticides on food and fibre crops and because of the vital importance of Bt to organic and other farmers, we consider any loss of Bt, any diminution of its effectiveness to be unreasonable, against the public good and per se adverse."
Beth Burrows, Edmonds Institute

3.4.2.5 Wood Prairie Fram

"We have used foliar Bt tenebrionsis and Bt san diego for the past nine years in a successful organic pest management program designed to control the Colorado Potato Beetle. We use several practices in addition to Bt to control CPB such as trench traps, flame control and crop rotation. Without question by far the single most effective component of our CPB programme is Bt..... Our ability to continue to produce high quality Certified organic potatoes would be in serious question should transgenic-induced Bt resistance occur because of the approval and use of transgenic Bt potatoes. This very real likelihood is a very real threat to our livelihood and that of our employees."
Jim & Megan Gerritsen, Maine

3.4.2.6 American Seed Trade Association

"ASTA recognises concerns which have been expressed by EPA and public interest groups that resistance to Bt could result in the loss of available natural pest control tools....Our members, though, have an interest in maintaining the effective uses of our products for long-term use in farming." ASTA does not agree with the need for mandatory resistant pest management plans.
Dean Urmston, ASTA

3.4.2.7 Biotechnology Industry Association

"BIO supports EPA's regulatory oversight of novel plant pesticides under the Federal Insecticide, fungicide and Roddenticide Act. We have, however, voiced concern about the policy direction the Agency has taken in using section 3 to mandate certain resistance management activities on the part of the industry."
Alan Goldhammer, BIO

3.4.2.8 Arizona Cotton Research and Protection Council

"Large acreage refuges of 20% or more non Bt in close proximity to Bt fields are not compatible with the economics of cotton production in Arizona....Extensive field observations by ACRPC personnel statewide support growers reports that large blocks of non Bt cotton adjacent to untreated Bt acreage result in non Bt pink bollworm population levels that are difficult if not impossible to adequately control....Infield refuges show promise based on preliminary 1997 test data generated in Arizona, but flexibility in application is extremely important to fit widely divergent planting strategies and equipment options. Therefore both full row non Bt plantings and mixed seed options should be considered."

3.4.2.9 Monsanto

"We recognise the need for insect resistance management programs to protect this technology and we have been working on such programs for over a decade.......Monsanto believes that responsible, effective product stewardship is the key to protecting this technology and ensuring its durability....We have developed and implemented grower agreements, and demonstrated that they are an efficient and effective means to both educate growers and to motivate them to comply with insect resistance management programs......We believe that our multifaceted IRM programs are effective and will become even more effective as we continue to incorporate the latest findings into the recommended practices. We see no currrent need for a general change in the requirements for refuge size and placement across current crops, pests and geographies."
Graham Head, Monsanto

3.4.2.10 Mycogen

"The current thought, theory, and hopefully science has led us to consider a resistance management recommendation that centres around structured refugia and high dose expression.....any sound resistance management plan must be based on the best available science and to date preliminary data has given us a recommendation that reflects just that. There are still questions to answer, however, and we are currently in the midst of a multifaceted, multi-year IRM research programme.....Mycogen's position is that additional research is needed in order to understand how to successfully structure such a refuge......In the absence, then of any additional data to indicate that the development of resistance is imminent, is it not prudent to be patient and allow the research to proceed in a systematic manner?"
Diane Shanahan, Mycogen Corporation

3.4.2.11 Novartis

"For the 1998 growing season we recommend that growers follow the NC205 guidelines (which recommends a "flexible refuge of conventional maize acres based on variables in a growers region of the country"), including the refuge planting options presented in their publications. We believe the most effective way to implement this programme is through intensive grower education with our colleagues from the extension entomology community, in concert with an incentive based programme."
Jefff Stein, Novartis

3.4.3 Conclusion

Almost two years have passed since the scientific panel discussed these issues in Washington. The EPA has been unable to draw any conclusions because the panel was itself unable to agree on any recommendations. Greenpeace International, the International Federation of Organic Movements and the Center for Food Safety have now taken legal action against Carol Browner, Administrator of the EPA, for not fulfilling its legal obligations under the Act (FIFRA). Their complaint is summarised below:

United States District Court for the District of Columbia
‘This is an action to declare unlawful and enjoin certain actions of the defendant’s, and others acting under her authority, regarding the approval and registration of genetically

engineered plants expressing *Bacillus thuringiensis* (Bt) endotoxins. These actions include a series of arbitrary and capricious pesticide registrations of genetically engineered Bt plants and a failure to analyze the programmatic environmental impacts of those genetically engineered Bt plant registrations. Defendant's actions regarding the pesticide registration of genetically engineered Bt plants violates the statutes and regulations of the defendant's including the Federal Insecticide, Rodenticide and Fungicide Act (FIFRA), 7 U.S.C. § 136, et seq., National Environmental Policy Act (NEPA), 42 U.S.C. § 4321, et seq., the Administrative Procedure Act (APA), 5 U.S.C. § 551 et seq., and the Public Trust Doctrine.

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CHAPTER 5. REMAINING QUESTIONS

How can we ensure the long-term biological efficacy of biopesticides instead of putting them one by one on the pesticide treadmill and then losing them forever? We started by asking a number of questions about the implications of regulatory regimes, market structures and intellectual property rights. Did they make it easier or more difficult to sustain the biological efficacity of biopesticides such as Bt?

5.1 Intellectual Property Rights

The question of property rights can be considered as an aspect of market structures because all the property rights systems that apply to living things are basically a device for getting invented knowledge into the public domain, the quid pro quo being that the market structure is modified to the advantage of the inventor. Whether or not a Bt plant is really an invention involves a long argument. For the moment most Bt plants are the subject of patent claims that are heavily contested. Markets in which commodities are protected by intellectual property rights systems have been re-structured to the commercial advantage of one of the competitors and are no longer free markets in the classical sense. It is, in theory, an exchange of invented knowledge for protection, one of the few areas nowadays where protectionism is institutionalised within a free market economy.

The application of intellectual property rights to Bt cotton and Bt potatoes has resulted to date in a global monopoly owned by Monsanto. The EPA is on record that a monopoly situation makes the licensing and regulation of such crops much easier than is the case with Bt maize, where several companies are in intense competition with one another. However, what happens if US anti-trust legislation is applied to Monsanto? And what happens when all the Bt patents run out and any company is free to produce these Bt plants? Maybe the question is academic. Maybe we can rest assured that the insect pests will become resistant to the Bt crops long before the patents on them run out. But what does that then say about the patent system? Is it right that Monsanto should have a monopoly on Bt cotton and Bt potatoes for as long as they are biologically effective? Where is the quid pro quo?

5.2 Regulation

There is already a debate about how the Novartis Bt maize would have been evaluated in terms of the Revised Dir 90/220. Under Article 5, the following four articles (6-9) do not apply to any products under development covered by Community legislation which provides for a specific environmental risk assessment similar to that laid down in those articles. Those who agree with the responsible bodies in the USA - that Bt crops are both

GMOs and pesticides - would argue that Bt crops should be dealt with under the EU pesticide legislation as well as under Dir 90/220 but this is expressly refused by Article 5, which stupidly forces the responsible authorities to consider Bt crops *either* as pesticides or as GMOs. It will one day be deemed necessary to harmonise the US and EU approaches to the regulation of plant pesticides. If the issues were to be considered in scientific terms it is obvious that regulation is an environmental issue. The most obvious forum is the Biosafety Protocol, or failing that the Conference on Biological Diversity or UNED. However, the USA still refuses to sign the Convention on Biological Diversity and it was the USA, together with its minor allies - Australia, Argentina, Uruguay and Chile that wrecked the Cartagena negotiations on the Biosafety Protocol in February 1999. If the issues are to be considered in political terms and resolved according to power relations then the harmoinisation issue will be taken up by the World Trade Organisation. Like most other powerful organisations, the WTO likes to cloak its deliberations and decisions with a scientific veil but this should not be mistaken for economic realities. Ironically, it would be a step towards greater rationality, transparency and democracy in Europe if the USA were to use the WTO to force the EU into adopting its apprach to the regulation of plant pesticides.

However, harmonisation usually involves compromise. If in the future, the EU treats Bt crops as pesticides they will be dealt with under legislation for dealing with chemical and biological pesticides. The problem here is that the current legislation is incapable of dealing with most of the implications of plant pesticides and is therefore inadequate in its present form.

If Bt crops are considered as GMOs then the relevant part of the Revised 90/220 is Annex IIIB regarding genetically modified higher plants. Section D7 requires information on any toxic or harmful effects on human health and the environment arising from the genetic modification. Section D8 requires information on the mechanism of interaction between the genetically modified plant and target organisms and section D9 requires information on potentially significant interactions with non-target organisms.

Section G requires information on the control, monitoring, post-release and waste treatment plans, and specifically any measures taken to preserve a distance from sexually compatible plant species and to minimise or prevent pollen or seed dispersal, a description of the methods to be used for the post-release treatment of the site, a description of the post-release treatment methods for the genetically modified plant material including wastes, a description of monitoring plans and techniques, and finally, a description of any emergency plans.

Section H requires information on the potential environmental impact from the release of the genetically modified plants, especially the likelihood of the plant becoming more persistent than the recipient or parental plants in agricultural habitats or more invasive in natural habitats, any selective advantage or disadvantage conferred to other sexually compatible plant species which may result from genetic transfer from the genetically modified plant, the potential environmental impact of the interaction between the genetically modified plant and possible target organisms, and finally, the possible environmental impact resulting from potential interactions with non-target organisms.

It can be seen that some of these clauses have been included in response to the complications arising from the development of herbicide resistant crops. However, as ever, the legislation lags behind the technical possibilities. Although a liberal interpretation of the intention behind the Directive could conceivably lead to the adequate control of Bt crops, there is nothing in any of the proposed legislation that deals with the management of insect resistance to such genetically engineered pesticide crops. Given the dismal track record of some responsible authorities - notably the British - under Dir 90/220, in which the narrowest possible interpretation of the legislation has been used to avoid discussion of any difficult environmental issues, the Revised 90/220 does not augur well for the management of Bt crops.

The interaction between the use of Bt sprays and the sowing of Bt crops in the same vicinity is already the subject of a copious scientific literature in the USA and informs the policy proposed by the EPA for the management of Bt crops. The European Union seems intent on bureaucratically separating the two forms in which farmers use Bt so that sprays are dealt with under the Pesticide Directive and crops are dealt with under the Deliberate Release Directive 90/220. This is patently counter-productive and can only possibly lead to the early loss of Bt as an insecticide.

As and when insect resistance to Bt crops becomes a problem in Europe, the legislation will be capable of dealing with it only if the European Commission insists on the emergency withdrawal of the crop as a condition of registration, either under Annex III(G)5 or under Annex IV(B)1.

In the USA there is a healthy and vigorous debate as to whether resistance management strategies for Bt crops should be mandatory or voluntary. In the EU, Annex IV of the Revised Dir 90/220, which deals with the market, merely states that "the following information shall be provided, when relevant ....in accordance with Article 11 of this Directive:
1. measures to take in case of unintended release or misuse
2. specific instructions or recommendations for storage or handling"
This paragraph could be interpreted as meaning a voluntary, as opposed to a mandatory set of recommendations to farmers regarding the planting of refuges, the use of other pesticides or any of the other measures already advocated by the responsible authorities in the USA.

It is surely ludicrous that the bacterium Bacillus thuringiensis is dealt with under separate legislation and separate departments of government, depending on whether it is used as an external or internal application, yet this is exactly what happens in the EU. The situation is even more ludicrous when one considers that the internal (genetically engineered) use of Bt has clear environmental and agricultural implications for its external use, whilst its external use can also have implications for its internal use. The current EU Directives are inadequate for regulating the use of Bt either as sprays or as genetically engineered Bt plants. In Chapter 3. we drew attention to the observations made by the EPA on the complex functioning of markets where several competing companies are selling the same Bt plant species. The EPA has already re-structured the US market for Bt maize hybrids by prohibiting the sale of newer Bt hybrids in certain parts of the USA. The EPA has also made it clear that the regulation of Bt potatoes and Bt cotton is made much easier by the fact that a single company currently has a monopoly of the US market.

The implication for Europe is clear. If the European Commission were prepared to structure the market for Bt plant species so that the company with the first registered product was given monopoly control of that market, there is at least some chance that the company might behave responsibly. The company could be obliged to ensure that its sales are geographically structured to gain the best possible management of insect resistance and thus ensure the long term biological efficacy of their product. Quite by accident, Novartis actually has a monopoly of the market for Bt maize in Europe, given that all other applications are currently blocked. However, this effective monopoly has not exactly led Novartis to adopt a policy of ‘responsible stewardship’ but rather the opposite. In Europe Novartis shows no inclination whatsoever to follow any of the precautionary practices that it is obliged to follow by the EPA in the United States.

5.3 Market Restructuring

It is clear that both the existing EU Directives and the European market structures encourage, at best, ridiculously short-term policies for the use of biopesticides, and at worst, guarantee that biopestides are quickly placed on the pesticide treadmill. It is possible that some re-structuring will be forced upon the European Commission and member States by legal challenges that have not yet been heard by the Courts. If the Courts determine that various bodies have acted unreasonably or unlawfully by not considering the Bt toxin expressed by Bt plants as a toxic substance, it will in future be necessary to consider Bt plants under both the GMO and the Pesticide legislation. This would be a considerable improvement on the present position. The European Union could do worse than simply adopt the definitions and procedures that have already been developed by the EPA in Washington. What is really needed, however, is a thorough re-thinking of pest management strategies that looks beyond the short-term military analogy of the agrochemical industry and has some hope of providing the world with food security into the future. Whilst lip-service is given to Integrated Pest Management, the EU legislation makes it all but impossible to restructure along such lines.

We noted in Chapter 2.6 that there are at least 15 possible tactics for slowing down insect resistance to Bt. According to Whalon (1992) "The possible tactics for resistance management include many options. None offer clear advantages in all environments and with all pests, except, perhaps, tactics that encourage survival or immigration of susceptible genotypes. Regardless of the approach used, resistance management becomes very complex where tactics must be co-ordinated against a pest on more than one crop or against more than one pest species." The EPA has allowed itself to be corralled by the industry into serious discussion of only two of the 15 strategies - a combination of tactic 7 (high dose) and tactic 14 (spatial refuge). Some of the other possible tactics are currently outside the technical reach of the industry but it is significant that strategies 7 and 14 fit neatly into the military paradigm and that those tactics that derive from a holistic paradigm are largely ignored. This is no accident; the holistic paradigms can only be profitable to the agrochemical industry if they have a monopoly of the market for the range of different products and strategies required by a successful IPM programme. It is also no accident that when a company like Monsanto finds itself in a monopoly position it seems to start behaving according to its longer term interests and thus with a good deal more concern for environmental concerns than is otherwise the case.

It is generally thought that the high toxin/refuge strategy should be able to delay the onset of resistant insects but it is no solution to the problem. Everyone agrees that resistance will set in due course. It might well be precisely because the strategy is doomed that the agrochemical industry finally seems to be willing to adopt such measures. In the USA on 21 September 1998 Novartis Seeds suddenly changed tack by announcing plans "to enhance its insect resistance management (IRM) stewardship" program for its NK(R) Brand Bt corn by offering customers a financial incentive for following the company's recommendations. "We made headlines last year as the first seed company to publicly support a science-based IRM strategy," recalls Dan Hinderliter, corn product manager for Novartis Seeds. "This year, we're going one step further by rewarding customers who chose to follow our IRM program." Called the Bt Stewardship Program, the financial incentive varies based on the quantity of NK Brand YieldGard(R) or KnockOut(R) corn seed purchased. Growers who buy a significant amount of Bt seed will receive substantial savings if at least 20 percent of their order includes non-Bt hybrids.

"With this program, we're offering to share IRM stewardship responsibilities with our customers so we can preserve this technology for years to come," Hinderliter explained. The voluntary program comes as Bt corn acres continue to rise. In 1996, Bt corn accounted for less than one percent of all U.S production; two years later, that number has risen to 19 percent. As Bt corn acreage increases, so does the need for farmers to adopt IRM strategies to prevent insects from developing resistance to the Bt protein expressed in NK Brand Bt corn."

Today, most entomologists believe maintaining a non-Bt corn refuge is the most effective approach to achieve this goal. Novartis Seeds worked closely with university scientists to develop the refuge strategies. As a result of their five-year collaborative effort, the company adopted the guidelines outlined by the Research and Extension Entomologists of the North Central Regional Research Project (NC205). Novartis Seeds and its associates remain the only major seed company to advocate that its customers follow those guidelines.

"We didn't make an IRM recommendation until the scientific community developed a research-based recommendation," Hinderliter acknowledges. "But once they reached a consensus, we quickly adopted their recommendations as our own. Today, those guidelines remain the best available, so for 1999 we continue to encourage our customers to follow that resistance management program."

The NC205 report recommends a flexible refuge of traditional corn acres based on variables in a grower's area. The scientists concluded that the actual amount of Bt refuge should vary between regions, farms and corn production systems. For example, the NC205 committee recommends a 20 percent refuge for Bt cornfields where the conventional corn refuge will not be sprayed for European corn borer. If the conventional corn sanctuary will be sprayed for corn borer, the recommended refuge area increases to 40 percent of the total Bt corn acres.

According to one observer, "Novartis are now having to offer payments to farmers to adopt complex management programmes hurriedly introduced in a desperate attempt to maintain the intended efficacy of their own technology. No supply merchant offers payments or discounts to farmers unless he has to. This can only be an indication of the level of concern held by Novartis that this technology is in danger of becoming unsustainable very quickly. Novartis states: "We didn't make an insect resistance management recommendation until the scientific community developed a research-based recommendation", a clear admission that the technology was introduced before there had been adequate research on key questions.

When the high dose/refuge strategy fails we will be left with the low toxin/marginal use strategy which is unattractive to the agrochemical industry because no one can see how to make money out of it, even if they held a monopoly of the market for a particular crop.

5.4 The Need for a Moratorium

There is, of course, one final strategy that neither Whalon nor Gould have mentioned: one could simply place a moratorium on Bt crops until such time as there is a consensus between ecologists and economists that there are regulatory/market structures in place which are adequate to the task of using biopesticides (and pesticides) in a sustainable way. This should be the policy objective of the European Union and until such time as these conclusions are reached, pesticides and biopesticides will continue to become biologically useless, pests will continue to increase their ability to compete with humans for food, and the security of our food systems will continue to be undermined.

For the moment, the European Union is in a complete mess about Bt crops. In so far as there is any EU policy, it indicates a more or less complete ignorance of American experience with the same issues. This is reprehensible because there is much that could usefully be learned about Bt from Washington. It is also stupid because the same companies operate on both sides of the Atlantic. There is administrative confusion in the European Commission and political disarray in the Council of Ministers. The European Parliament is capable of reflecting public concerns but its warnings have been ignored by the Commission.

Whilst the European Commission shows no signs of taking clear responsibility for the management of Bt crops, the lack of proper management will almost certainly serve to accelerate the onset of insect resistance. As things stand, there are good grounds for predicting that the European Corn borer will become resistant to Bt maize in Europe before it does so in the USA. The Novartis Bt 176 maize is the only Bt crop that has been commercialised in Europe. According to American entomologists, it is the Bt crop that is most likely to result in insect resistance. In addition, Novartis is neither obliging nor encouraging farmers to adopt any resistance delaying tactics in Europe. Between them, Novartis and the European Commission seem to be encouraging the development of a new form of Ostrinia nubilalis which is resistant to Bt. Should it be called Ostrinia nubilalis novartis or Ostrinia nubilalis ec?

5.5 Postscript - after Bt there is PhL and after PhL?

The agrochemical industry shows no signs of having learned anything from the Bt story, and is therefore set to repeat its errors and continue damaging our environment. It is not necessary to look very far for examples of gung-ho military madness.

Here are a couple of recent examples:
"........ we are witnessing a truly revolutionary time in agriculture. Transgenic plants expressing Bt toxins provide a level of insect control not seen since the introduction of chemical insecticides decades ago. Unlike the release of new technologies in the past, we in industry and academia are keenly aware of the need to manage resistance in insects to this promising new technology. Accordingly, other non-Bt proteins are being identified that will be used in combination with, or in place of, Bt as one component of resistance management. As exciting as this first generation technology is, it pales in comparison to the second and third generation technologies under development. We can expect to see in the future "smart-proteins" designed and constructed by protein engineering that will specifically target even our most problematic pests. Finally, the ability to engineer plants to produce novel non-protein compounds will provide crop pest managers with an almost limitless number of options for controlling insect pests."
ENGINEERING INSECT RESISTANT PLANTS: BT AND BEYOND
Joseph E. Huesing, Northrup King Co.

"For thirty years Bt...has been a pest-control mainstay for foresters, farmers, gardeners and homeowners in search of a safe, natural way to neutralise the bugs that bug them.........Now a team of scientists from two laboratories at the University of Wisconsin at Madison, working in collaboration with DowElanco of Indianapolis, hopes to unleash a new bacterium with similar insect-thwarting properties.

"Its a voracious pathogen. One bacterial cell can kill an insect", says Jerald Ensign a UW-Madison professor of bacteriology. The bacteria live inside the gut of nematodes that invade insects. Once inside an insect host, the bacteria are released from the nematode, kill the insect and set up rounds of bacterial and nematode reproduction that turns the insect into a protein soup, food for large numbers of nematodes.

The discovery of a diverse new family of insect-killing bacteria has added importance since, in recent years, some insects have already begun to exhibit resistance to the Bt toxin, raising fears that the biological pesticide may be losing its potency. By adding an entire family of lethal bacteria to the biological pest-control arsenal, the Wisconsin and DowElanco scientists have opened a potentially broad new front in the war on insect pests since each of the Photorhabdus strains produces its own variation on the toxin.

"What we have is a natural source, almost an infinite variety of toxic molecules", says Ffrench-Constant. "We cant afford to hook ourselves to a single bacterium or a single toxin."

The next step already well underway, is to move those genes to any amenable crop plant. The need for Bt replacements is critical before we have many crops in North America expressing a limited range of Bt toxins. If we don't have them its an open invitation for natural selection to confer resistance on insects and we'll lose that control."
"PhL - A NEW INSECTICIDE KING?"
by T. Devitt in Wisconsin Week 14.1.1998

Will they ever learn?
Can they be stopped?