# Sustainable Use of Genetically Modified Crops in Developing Countries

*Fred Gould and Michael B. Cohen*

When potential risks to the environment from new genetically modified (GM) crops are discussed, the focus is generally on risks of genes escaping to wild relatives that become "superweeds," risks of crops themselves becoming weeds, and the potential that toxins produced by the GM crops (or toxins used to kill pests of engineered crops) will harm nontarget organisms (for example, Johnson, This volume; Rissler and Mellon 1996; Snow and Moran Palma 1997) . These are all tangible risks, that can be diminished if taken seriously. Their worst-case negative impacts on the overall environment in developing countries are relatively small compared to the impact on the environment of rural populations without food security and living in poverty.

Because poverty can lead to environmental degradation, we will examine a potential chain of interactions between genetic modification, increased yield, variation in yield, food security, and environmental degradation. We believe that new genetic modification has great potential for increasing yield and decreasing yield variation, but that such accomplishments will require vigilance by scientists and society.

Giving farmers the right kind of seeds can never ensure food security, but giving them the wrong kind of seeds always can make things worse. Social scientists know that you cannot alleviate poverty just by growing more food, but agricultural scientists are always being pushed by philanthropic and development organizations to produce more food because food production is a necessary but not sufficient condition for food security (Serageldin 1999). This has led to increased yield becoming a focus of international attention.

About 50 years ago agricultural scientists were told that the growing world population would demand that we substantially increase crop yields. Amazingly, agricultural scientists, with the financial aid of many government and private organizations, did a reasonable job of meeting this demand (Conway 1998). Today agricultural scientists are being told to do this again because world population growth by the year 2025 or so will demand that we increase production by 30-50 percent (see Pinstrup-Andersen and Cohen, This volume). A special report in Science (Mann 1999) reviewed recent debates about whether, with or without biotechnology, plants could be pushed to become that much more productive. Even if agricultural science can push plants and soils to meet this demand, what happens in 2025 if the optimistic forecasts of no population growth after that date are incorrect? Do we once again ask agriculturalists to raise yields?

## Importance of Yield Stability

One thing that crop and animal breeders have learned over the years is that when you select strongly for improvement in one trait of an organism, be it speed in a race horse, appearance in a dog, or yield in a crop, there are tradeoffs (Falconer and Mackay 1996; Mann 1999). The race horse may be frail, the dog less intelligent, and the crop less capable of dealing with stress. In our efforts to keep increasing maximal or average yield, we must be vigilant not to produce crops that have high variation in yield because they are less capable of withstanding stresses associated with unusual weather or pest outbreaks. There has always been support given to programs that breed for stress resistance, but these programs are often funded with the goal of increasing yield rather than decreasing variation in yield. A number of recent reviews have attempted to determine if the variation in crop yields (statistically adjusted for change in the mean) have changed during the 20th century. The conclusions of these assessments indicate that on a global and continental level overall adjusted variation in yield has not generally increased (Naylor, Falcon, and Zavaleta 1997; Calderini and Slafer 1998), but that the component associated with genetic crop improvement has increased (Calderini and Slafer 1999). This means that the variation in yield is being pushed upward by the varieties of crops grown, but that other factors such as improved irrigation may be balancing out this increase caused by breeding.

Unpredicted spatial and temporal variation in yield has a different relative importance depending on your perspective. Local variation in yield gets partially averaged out at the world market scale, and it can be dealt with reasonably well by individual farmers if they have the resources to farm on a three or four year time horizon. But for the subsistence farmer, variation in yield can be critical. If you were a subsistence farmer who could not save harvested corn for more than 12 months, would you rather have a corn cultivar that in five successive years produced 48, 72, 12, 24, and 84 bushels per hectare or a second cultivar that produced 46, 36, 41, 43, and 38 bushels per hectare? Your choice would probably depend greatly on the details of your social and economic situation (for example, whether you had alternative crops or alternative sources of income, and whether you had cash crops; Walker 1989), but in many cases your concern over the 15percent lower average yield of the second cultivar would not outweigh concern over the year when the first cultivar yields 12 bushels per hectare, especially if you could not predict when that year would come. Having the right seed cannot ensure that you will not have variation in yield, but having the wrong seed can guarantee that you will have high variation. The "race horse" seeds we produce for resource-rich farmers may not always be the best seeds for subsistence farmers. Our contention is that there is a need to pay substantially more attention to yield stability as we strive for higher average yields. A more radical stance is that increasing yield stability rather than increasing average yield should be the primary goal.

Because at the local level, drought, flooding, and pests vary significantly from year to year, cultivars bred with resistance or tolerance to any of these disruptive factors would decrease yield variation and could also result in increased average yield. Genetic engineering has improved and should continue to improve, these traits, but care must be taken in how this is done if a major goal is decreased variability in yield.

### Pest Resistance Management and Yield Variation

Crop breeders have long known that some conventionally bred cultivars with resistance to insect and microbial pests may perform wonderfully for the first few years after they are deployed commercially, but then fail miserably in controlling the targeted pests in later years because the pest has evolved a way to cope with the resistance mechanism in the cultivar. Sometimes there is a slow decline in effectiveness of the cultivar, but in other cases the onset of control failure is rapid and unpredictable. If you are a subsistence farmer, the failed performance of such cultivars can mean hardship, especially if the cultivar had previously performed well and long enough for you to gain confidence in it. Indeed some of the criticisms of the Green Revolution of the 1960s and 1970s centered on rice cultivars that were rapidly adapted to by insect and microbial pests. For example, brown planthopper populations adapted to the single-gene resistance in the first Green Revolution rices within 2-3 years of their widespread cultivation (Gallagher, Kenmore, and Sogawa 1994), and single-gene resistance to the rice blast fungus has been notoriously unstable (Ou 1985). The longevity of cultivars with single blast resistance genes in Japan has been less than 3 years (Kiyosawa 1982).

In industrial countries, breeders and seed producers sometimes try to deal with pest adaptation to widely used crops that have one resistance mechanism by maintaining, in reserve, replacement cultivars with different resistance mechanisms, for example wheat rust (McIntosh and Brown 1997). These systems are sometimes able to replace cultivars in a single season as was the case with the southern corn blight epidemic in the USA. In developing countries, instituting such a system for subsistence crops is difficult or impossible because of limited infrastructure and resources.

Not all pest-resistant cultivars are rapidly adapted to by their target pests. Entomologists and plant pathologists have worked hard to predict whether a specific resistant cultivar is likely to work well for a long time under field conditions. This characteristic called "durable resistance" has proven to be partially predictable, but many plant pathologists are only willing to judge the durability of a specific type of pest resistance in retrospect.

The general problem of pests adapting to any approach used to control them has been the bane of agriculturalists for centuries. Weeds, pathogens, and insects have all overcome various cultural, chemical, and biological approaches used for their control (Gould 1991). Over 500 insect species are known to have adapted to at least one insecticide (Georghiou and Lagunes 1988), and it often takes less than three years for this adaptation to evolve (Forgash 1984). In many developing countries this can severely disrupt food production because replacement insecticides are often not available, and the beneficial insect populations have been decimated by insecticide use.

In 1997 and 1998, there was a tragic series of over 400 suicides among cotton farmers in Andra Pradesh, India in response to crop failures that were in part the result of pest adaptation to insecticides (Verma 1998; McGirk 1998). The farmers were heavily in debt because of several seasons of crop failures, caused by irregular rainfall and heavy infestations of the insect pests *Spodoptera litura* and *Helicoverpa armigera*. Application of large doses of highly toxic insecticides such as monocrotophos and methomyl were not effective because of pest resistance to these compounds, and their toxicity to predatory and parasitic arthropods which otherwise could have provided some level of natural biological control.

In the 1970s entomologists, plant pathologists, and weed scientists began a concerted effort to use knowledge of evolutionary biology and population genetics to develop strategies for slowing the rate at which pest populations evolved adaptations to control tactics such as pesticides and pest-resistant crops. This approach called "pest resistance management" now seems highly appropriate for crops developed using genetic engineering, because there is good reason to predict that some approaches to the development and deployment of engineered pest-resistant crops will last much longer than others.

## Bt Crops as a Case History

When new genetically improved crops that expressed insecticidal proteins from *Bacillus thuringiensis* (Bt) were first developed, there was much concern in the United States about insects adapting to these toxins. Unlike conventionally bred resistant crops, where a resistance mechanism can only be moved within a single crop species, the Bt toxins were being moved into multiple crops, so insects that fed on more than one crop would get multiple exposures. Unlike insecticides that are sprayed only during some time periods in the season when pest pressure is high, the newly developed crops produce the toxin all season long, so all insects in a population can be exposed to the toxin. Everything known about pest adaptation indicated that overuse of such crops could give great control for a limited number of years followed by failure (Tabashnik 1994).

In the United States there was one other pertinent fact about Bt crops. *B. thuringiensis*, the bacterium that was the source of the toxin genes in the crops, has long been sprayed on crops by organic farmers and others as an alternative to chemical insecticides. Organic farmer groups and their supporters protested that the overuse of Bt toxins in genetically engineered crops, and the subsequent development of adapted pests, would leave them without an effective pest control tool. This highlighted two issues: one was the plight of the organic farmer and the other was the unique, environmentally benign nature of Bt toxins compared to conventional pesticides. A set of

Bt toxins, sometimes referred to as Bt endotoxins, were known from previous uses to be effective at killing either some caterpillars or some beetle species, but they had no effect on almost all other species. From an environmental perspective these are wonderful toxins, and unless other toxins with this high target specificity can be quickly found, the overuse and loss of Bt toxin efficacy in transgenic crops could send cotton and potato farmers back to spraying environmentally disruptive chemicals.

All of the above issues led the United States Environmental Protection Agency (US-EPA) to finally require that Bt crops be developed and deployed in a manner that would decrease the risk of rapid pest adaptation. EPA staff have worked hard in pushing companies to develop workable resistance management plans (Matten 1998), but to date this has only been partially successful. It is worth examining some of the processes that led to the current situation in the United States to understand better some of the issues that will face developing countries if they attempt a similar approach. We are not privy to all of the workings of the US-EPA so we can only provide an observer's perspective.

## Bt-Resistance Management

Prior to the commercialization of any genetically improved crops, the US-EPA held meetings of Scientific Advisory Panels to get advice from experts outside EPA regarding risks of genetically improved crops. One of the recommendations of these panels was to institute resistance management programs. When EPA granted conditional registrations for the first Bt corn cultivars in 1996, one of the conditions was the development of resistance management plans by the year 2000. The EPA felt that such plans were not immediately needed because they expected adoption of these Bt cultivars to proceed more slowly than it actually did. The conditional registration for Bt cotton included a resistance management plan, but this plan is now being reexamined because it lacks rigor. More recent conditional registrations of newer corn cultivars have included more stringent resistance management plans. The imposition of resistance management plans is something new for the US-EPA and the agency has been gaining sophistication in this area over time.

In 1998 the EPA convened a Scientific Advisory Panel to reassess the issue of Bt resistance management. The report of this panel (EPA 1998) laid out some clear recommendations to the EPA. After considering a number of potential resistance management strategies, the panel recommended that "a refuge/high dose strategy must be employed for target pests within the current understanding of the technology." They added that "regulatory strategies should serve to provide growers with a sustainable approach that encourages compliance." These were important recommendations worthy of careful examination.

We would like to discuss the refuge/high dose strategy in some detail because it is often misunderstood. The high dose portion of this strategy is most easily understood by analogy to the use of antibiotics. When doctors prescribe antibiotics they often give their patients the admonition that even if they feel completely cured after three days, they should continue to take the antibiotic for the full time prescribed. The reason for this is to produce a high dose of antibiotic for an extended time period that will kill even those rare bacterial cells that have a mutant gene conferring partial tolerance of the antibiotic. After three days you may have killed 99 percent of the targeted bacteria, but if the 1 percent that survive have a gene that confers partial tolerance and are transmitted to another individual, his or her infection will be more difficult to treat. More importantly, when that next individual takes the antibiotic, the partially tolerant bacteria may evolve even higher tolerance if among the millions of bacteria involved in the infection there are a few bacteria with other mutations that add to the tolerance conferred by the initial mutation. When a patient takes an antibiotic for the full period prescribed, the expectation is that even the partially tolerant bacteria will be killed. As long as it takes more than one evolutionary step to result in complete tolerance of the antibiotic, the prolonged use of the antibiotic should derail the adaptive process by inhibiting the first step.

The use of a high dose of Bt toxin in crops serves a similar (though not identical) purpose. In all cases studied to date it takes more than one gene, or at least more than a single copy of a gene (heterozygous condition) to confer high tolerance of Bt toxins (Tabashnik 1994; Shelton and Roush 1999). When Bt crops are first commercialized it is estimated that about 1 in 1000 individuals may carry one copy of a gene for tolerance of Bt, and only 1 in 1 million would carry the two copies needed to achieve a high level of tolerance (Gould and others 1997). The high dose approach is set up to ensure that each plant that produces Bt toxin produces enough to kill most of the partially tolerant individuals.

But if the high dose is used by itself, some insects out of the billions that can infest a local area may have two copies of the gene. If they survive and mate, the Bt crops could rapidly lose effectiveness. This is where the refuge part of the "refuge/high dose" approach comes in. All of the current target insects for Bt crops are obligately sexual. That means that they must mate to reproduce, and that their offspring obtain half of their genes from each parent. If a small portion of a farm is planted to a cultivar that does not produce Bt toxin this area serves as a refuge for Bt-susceptible insects. Because the highly tolerant insects are expected to be so rare, they are likely to mate with susceptible insects produced in the refuge. The offspring of these matings will have only one gene for tolerance, and so will be killed if they feed on a Bt-producing plant. By combining the refuge and the high dose, this strategy derails the evolutionary process as long as more than one gene copy is required to survive the high dose. Pests can eventually adapt to such a strategy but the time period required can be 10 to 100 times longer than expected if this strategy is not implemented.

The 1998 EPA Scientific Advisory Panel was clear about what constitutes a high dose and what constitutes an effective refuge. They defined a high dose as 25 times the amount of toxin needed to kill susceptible target insects. They concluded that an effective refuge existed when for every insect with a resistance gene produced in the Bt crop there would be 500 susceptible insects produced that could mate with the resistant insects. These are stringent requirements and they work in concert. If a crop does not quite produce a high dose, the expected number of insects with at least one resistance gene increases. This results in the need for a larger refuge to produce the 1:500 ratio.

How do these recommendations line up with Bt crops that are now on the market in the United States? With Bt potato the data indicate that there is a high dose for the target pest, Colorado potato beetle (Perlak and others 1993). However, it is not confirmed that farmers are planting effective refuges. With corn, most cultivars produce a high dose for the European corn borer, but not for the corn earworm (Andow and Hutchison 1998). Refuges currently appear large enough for the European corn borer, in part because of lack of full adoption of Bt corn, but the refuges may sometimes be too far from the Bt corn to allow insects from the refuge to cross-mate with insects from the Bt crops. In cotton there is a high dose for the tobacco budworm (a major cotton pest) but not for the corn earworm (also called the cotton bollworm in cotton) (Gould and Tabashnik 1998). Proposed refuges of about 10 percent are expected to be sufficient for the tobacco budworm, but may not be sufficient for the cotton bollworm. There appears to be a high dose in cotton for the pink bollworm, but this has not been completely confirmed. There is certainly room for improvements when the producers of Bt crops present their new resistance management plans to the US-EPA in 2000.

### *Implications for Developing Countries*

If the United States is struggling to meet the requirements for resistance management plans, what does this mean for developing countries? Monsanto has already entered joint ventures in China to produce Bt cotton. At a recent USDA/EPA workshop (August 1999, Memphis, TN), there was debate as to whether similar resistance management strategies would be required in China. The expert statement was conditioned on the assumption that no Bt corn was grown in China. If that assumption held then the targeted Chinese pest on Bt cotton, *Helicoverpa armigera*, could utilize non-Bt corn to produce the Bt-susceptible insects. It appears that there now will be Bt corn grown in China, and the Bt cotton that is being planted in China does not have a high dose for the target insect. This is not the kind of scenario that is likely to retard the evolution of adapted pests. If Chinese farmers and administrators come to rely on Bt corn and cotton in the next few years using the current technologies and risk management, there is a clear risk that yields will show variation over time. (It is important to note that one reason that Chinese farmers need

Bt cotton is the fact that the target insect pest, *Helicoverpa armigera,* has adapted to conventional insecticides and can not be effectively controlled.)

There is economic pressure in many developing countries to adopt Bt crops that were developed to control U.S. pests. If these crops are sold as "second hand" cultivars to these countries, it is hard to imagine that they will usually be effective at thwarting pest adaptation. Unless there are careful contingency plans to deal with the eventual failure of these cultivars, their adoption by developing countries could lead to higher than necessary yield variation. For example, it has been argued that situations such as that in Andra Pradesh demonstrate the urgent need for the release of Bt cotton in India. Two kinds of Bt cotton have been field-tested in India: one from the Monsanto Company and one produced by an Indian research institute. Many farmers will be eager to adopt Bt cotton, which can help to control *S. litura* and *H. armigera*. The availability of Bt cotton may also attract many new farmers to invest in growing cotton. However, if a carefully designed resistance management plan is not implemented, the farmers may suffer another severe setback in a few years should the pests adapt to the Bt cotton. In desperation, these farmers may again turn to highly toxic insecticides, repeating a tragic cycle.

It is often said that by the time insect pests adapt to Bt crops, biotechnology will develop replacements. If it was easy to develop replacements, competitive market pressures in the U.S. cotton and corn seed trade would have already resulted in alternative toxins being produced. The only even marginally novel toxin in corn is the Cry9C Bt toxin that AgrEvo has marketed, but because of health concerns, the US-EPA has approved its use only in corn grown for livestock feed. It has been said that the people with the most to lose from pest adaptation to Bt toxins are those who own the companies that own the genetically engineered seeds, but the aggressive stances of some companies against implementation of resistance management plans recommended by US crop scientists does not, however, indicate sincere concern. An explanation for this discrepancy could be that as with the pesticide market, most of the important profits from Bt crops are expected to come in the first years of widespread use, and resistance management could interfere with these early profits. Public and commercial interests are therefore expected to classh.

### *Bt Resistance Management in Rice*

International agricultural research centers such as IRRI (International Rice Research Institute) have devoted significant resources into development of resistance management strategies. At IRRI, research has led to a much better understanding of the type of Bt rices and cultivar deployment strategies that will be needed to arrest adaptation to Bt rices by two major stem- boring pests (Cohen and others 1997). It is clear from this research that even if high dose plants can be developed, it will be difficult to institute effective refuge systems in subsistence, rice growing systems. Seed mixtures of a Bt and non-Bt varieties will be easier for farmers to establish, but studies of the biology of the target pests indicate that field-to-field refuges will be more effective (Cohen et al. 1997; A. Dirie, N.L. Cuong, M.B. Cohen, and F. Gould, unpublished data). In some industrial countries, it has been possible to legislate and enforce the use of refuge fields by farmers growing Bt corn and Bt cotton (Andow and Hutchinson 1998, Gould and Tabashnik 1998). It will presumably be quite difficult to implement the use of refuges by farmers in developing countries, where farm sizes are small, the numbers of farmers is very large, and there is limited communication with farmers through extension agents or other means.

The best way to get around the problem of less than optimal refuges is to build reinforced high-dose cultivars. So far, the best way to do this seems to be by producing cultivars with high doses of two types of toxins that each require a different adaptive mechanism in the insect pest (Gould 1991; Roush 1997). For an insect to survive on such a plant, it would need to carry mutations at two genetic loci, one conferring resistance to each toxin. Insects with two copies (homozygous) of the mutations at both loci will be rare in pest populations that have had limited or no previous exposure to the toxins. Thus smaller refuges would suffice to prevent mating between two resistant individuals. For example, with a variety that produces two toxins it might be sufficient for a village to have 5 percent of its fields planted to non-Bt varieties, compared to the 25 percent refuge that might be necessary to provide good resistance management for a Bt variety that produced only one toxin.

For varieties genetically engineered with two toxins, it would be ideal if one toxin was a Bt delta-endotoxin (the class of toxin used in all Bt crops produced so far), and the second was from an unrelated class of toxins. Unfortunately, as noted above, additional classes of toxins that have all of the advantages of delta-endotoxins have been difficult to find. The best that can be done at present is to select pairs of delta-endotoxins that are highly dissimilar in amino acid sequence (some pairs of toxins sharing as little as 20% amino acid similarity, Feitelson, Payne, and Kim 1992) and that have been shown to bind to different target proteins in the midgut of the insect pest (Van Rie 1991; Gould 1991). Such combinations of toxins have been identified for several important pests (Gould 1998). Unfortunately, in at least two pest species, strains have been identified that have broad-spectrum resistance to widely divergent delta-endotoxins (Gould and others 1992; Moar and others 1995). In addition, given that industrial countries are having difficulty in developing alternative toxins, this will certainly be a high hurdle for international research centers and national agricultural research systems, unless assistance is received from industrial countries in the form of substantially increased research funding or donation of patented technology

## Regulatory Requirements

The development and implementation of any resistance management plan in developing countries will require action by national biosafety committees, departments of agriculture, or other regulatory bodies. National biosafety committees in developing countries have made impressive progress in drafting and implementing biosafety regulations for the importation and testing of transgenic crops. For example, within the past 10 years regulations for field testing have been established by China, India, Thailand, and the Philippines. Regulators in developing countries have shown an awareness of the importance of resistance management, but have not yet faced the challenge of producing a specific plan for a specific Bt crop. As Bt crops begin to approach commercialization in developing countries, it is important that international organizations such as ISNAR (International Service for National Agricultural Research) and others, which have helped to train national biosafety committee members, expand coverage of the resistance problem in their training courses and workshops.

## Conclusion

In the above discussion we have only touched on some of the problems inherent in developing pest-resistant cultivars that can be expected to sustainably decrease yield variation. While it will not be difficult to spread pest resistant cultivars around the world in the next few years, it will be difficult to do this in a way that increases long-term food security and thereby decreases environmental risks. We must soon decide if sustainable pest-protected crops will be a priority in international agricultural research.

## References

Andow, D., and W. Hutchison. 1998" Bt-corn resistance management." In: M. Mellon and J. Rissler, eds. *Now or Never: Serious New Plans to Save a Natural Pest Control.* Cambridge MA: Union of Concerned Scientists.

Calderini, D. F., and G. A. Slafer. 1998. "Changes in yield and yield stability in wheat during the 20th century." *Field Crops Res.* 57,335-47.

Calderini, D. F., and G. A. Slafer. 1999. "Has yield stability changed with genetic improvement of wheat yield?" *Euphytica* 107, 51-9.

Cohen, M.B., A. M. Romena, R. M. Aguda, A. Dirie, and F. L. Gould. 1997. "Evaluation of resistance management strategies for Bt rice." *In Proceedings of the Second Pacific Rim Conference on Biotechnology of Bacillus thuringiensis and Its Impact on the Environment*. Bangkok: Entomology and Zoology Association of Thailand.

Conway, G. 1998. In: *The doubly green revolution: food for all in the 21st Century* Ithaca, N.Y.: . Cornell Univ. Press.

EPA. 1998. FIFRA Scientific Advisory Panel. Subpanel on *Bacillus thuringiensis* (Bt) plant-pesticides and resistance management. Washington, DC.: EPA.

Falconer, D. S., and T.F.C. Mackay 1996. *Introduction to Quantitative Genetics*. 4th ed. London: Longman.

Feitelson, J.S, J. Payne, and L. Kim 1992. "*Bacillus thuringiensis* - Insects and beyond." *Bio/Technol*. 10, 271-5

Forgash, A. J. 1984. "History, evolution and consequences of insecticide resistance." *Pestic. Biochem. Physiol.* 22, 178-86.

Gallagher, K. D., P. E. Kenmore, and K. Sogawa. 1994. "Judicial use of insecticides deter planthopper outbreaks and extend the life of resistant varieties in Southeast Asian rice." In: R. F. Denno and J. T. Perfect, eds. *Planthoppers: Their Ecology and Management*. New York: Chapman & Hall.

Georghiou, G. P.,and A. Lagunes. 1988. The occurrence of resistance to pesticides: Cases of resistance reported worldwide through 1988 Rome: FAO. 325p.

Gould, F. 1991. "The evolutionary potential of crop pests." *Am. Sci*. 79,496-507.

Gould, F. 1998. "Sustainability of transgenic insecticidal cultivars: integrating pest genetics and ecology." *Annu. Rev. Entomol*. 443, 701-26.

Gould, F., and B. Tabashnik. 1998. "Bt-cotton resistance management." In: M. Mellon and J. Rissler, eds. *Now or Never: Serious New Plans to Save a Natural Pest Control.* Union of Concerned Sceintists, Cambridge MA.

Gould, F., A. Anderson, A. Jones, D. Sumerford, D. G. Heckel, J. Lopez, S. Micinski, R. Leonard, and M. Laster. 1997. "Initial frequency of alleles for resistance to *Bacillus thuringiensis* toxins in field populations of *Heliothis virescens." Proc. Natl. Acad. Sci. USA* 94, 3519-23.Union of Concerned Scientists.

Gould, F., A. Martinez-Ramirez, A. Anderson, J. Ferre, F. J. Silva, and W. J. Moar. 1992. "Broad-spectrum resistance to *Bacillus thuringiensis* toxins in *Heliothis virescens*." *Proc. Natl. Acad. Sci. USA* 89, 7986-90.

Kiyosawa, S. 1982. "Genetics and epidemiological modeling of breakdown of plant disease resistance." *Annu. Rev. Phytopathol*. 20, 93-117.

Mann, C. C. 1999. "Crop scientists see a new revolution." *Science* 283, 310-4.

Matten, S. R. 1998. "EPA regulation of resistance management for Bt plant-pesticides and conventional pesticides." *Resist. Pest Mngt*. 10,3-8.

McGirk, T. 1998. "Death in the countryside." *Time Magazine* June 22, 52.

McIntosh R.A., and G.N. Brown. 1997. "Anticipatory breeding for resistance to rust diseases in wheat." *Annu. Rev. Phytopathol*. 35, 311-26

Moar, W. J, M. Pusztai-Carey, H. van Faasen, D. Bosch, R.. Frutos, C. Rang, K. Luo, and M. Adang. 1995. "Development of *Bacillus thuringiensis* CryIC resistance by *Spodoptera exigua* (Hubner) (Lepidoptera: Noctuidae)." *Appl. Environ. Microbiol*. 61,2086-92.

Naylor, R., W. Falcon, and E. Zavaleta. 1997. "Variability and growth in grain yields, 1950-94: does the record point to greater instability?" *Popul. Develop. Review* 23, 41- 58.

Ou, S. 1985. *Rice Diseases*, 2nd ed. Commonwealth Mycological Institute. Kew, Surrey, U.K.

Perlak, F. J., T. B. Stone, Y. M. Muskopf, L. J. Petersen, G. B. Parker, S. A. McPherson, J. Wyman, S. Love, G. Reed, D. Biever, and D. A. Fischoff. 1993. "Genetically improved potatoes: protection from damage by Colorado potato beetles*." Plant Molec. Budoc*. 22, 313-21.

Rissler, J., and M. Mellon. 1996. *The Ecological Risks of Engineered Crops*. The MIT Press: Cambridge, Massachusetts.

Roush, R. T. 1997. "Managing resistance to transgenic crops," In: N. Carozzi and M. Koziel, eds. *Advances in Insect Control: the Role of Transgenic Plants*. London: Taylor & Francis.

Serageldin, I. "Biotechnology and food security in the 21st Century." *Science* 285, 387-9.

Shelton, A. M., and R. T. Roush. 1999. "False reports and the ears of men." *Nat. Biotech.* 17(9): 832.

Snow, A. A., and P. Moran Palma. 1997. "Commercialization of transgenic plants: potential ecological risks." *BioScience* 47, 86-96.

Tabashnik, B. E. 1994. "Evolution of resistance to *Bacillus thuringiensis*." *Annu. Rev. Entomol*. 39, 47-79.

van Rie, J. 1991. "Insect control with transgenic plants: resistance proof?" *Trends in Biotechnology* 9, 177-9.

Verma, J. 1998. "Cotton, pesticides, and suicides" *Global Pesticide Campaigner* 8(2), 3-5.

Walker, T. S. 1989. "Yield and household income variability in India's semi-arid tropics." In: J. R. Anderson and P.B.R. Hazell, eds. *Variability in Grain Yields*. Baltimore: Johns Hopkins Univ. Press.