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Review article

The international debate on the biosafety of genetically modified crops: scientific review of several cases of debate

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Abstract
There have been several major cases in the international debate on the biosafety of genetically modified (GM) crops, including the following. (i) The case of Pusztai's claim in 1998 that GM potato with inserted *gna* gene from snowdrop caused adverse effects on rat health. The peer review led by the UK Royal Society concluded that Pusztai's results were incorrect in many aspects and no such adverse effects should be inferred from them. (ii) In 1999, *Nature* published a paper by a group from Cornell University in which it was reported that the larvae of monarch butterfly were killed by the pollen of Bt corn on milkweeds. Subsequent laboratory and field studies have shown that pollen of Bt corn does not harm the monarch butterfly. The decline in population density of the monarch butterfly is caused mainly by the overuse of pesticides and environmental changes occurring in Mexico. (iii) In 1998, volunteer canola resistant to three herbicides was reported in a canola producer's field in northern Alberta, Canada, which was then called a 'super weed' by activists. In fact, 'super weed' is not a scientific term and no such case exists in nature: the triple-resistant volunteer canola can be killed by spraying with the herbicide 2,4-dichlorophenoxyacetic acid. (iv) In November 2001, Quist and Chapela published a paper in *Nature* claiming that DNA sequences similar to the *CaMV35S* promoter and *adh1* gene used in GM corn Bt 11 were found in samples of maize landraces collected from Oaxaca, Mexico. Subsequent scientific analyses demonstrated that the sequence of the 35S promoter detected was an artefact and the sequence of *adh1* was *adh1-F*, a native gene in maize and not the *adh1-S* transgene used in Bt 11. (v) In June 2002, Greenpeace published a report which stated 'Bt cotton damaged the environment in China'. The positive benefits of Bt cotton in China were not cited in Greenpeace's report. The fact is that, as a result of commercialization of Bt cotton, the amount of pesticides used for cotton bollworm control has been dramatically reduced by 70–80%. Therefore, the population size of predators and the diversity of arthropods in Bt cotton fields have increased drastically, which resulted in a dramatic reduction of the aphid population by 443- to 1546-fold in Bt cotton fields compared with non-Bt cotton fields. Monitoring bollworm populations nationwide in cotton-growing areas has shown that none of them has developed resistance to the Bt protein or to Bt cotton to date. The migration behaviour of the bollworm, the inheritance of insect resistance to Bt controlled by an incomplete recessive gene, the existence of 'natural refugia' in multiple-cropping systems in North China and the use of transgenic cotton with double genes (*Bt/CpTI*)

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have all played important roles in delaying the development of resistance to Bt cotton in bollworm populations. In conclusion, international debates on the biosafety of GM crops are not purely a scientific issue, but are related to economic and trade considerations.

Keywords: transgenic crops; biosafety; debate

Introduction

In recent years, dramatic controversy about the biosafety of genetically modified (GM) crops and misguided reports on the subject have negatively affected the public's acceptance of biotechnology products and the commercialization of GM crops. In this article, several cases in the international debate on the biosafety of GM crops are reviewed based on the scientific data available.

Before analysing the cases, the two different concepts of 'risk' and 'hazard/danger' should first be clearly defined. 'Risk' refers to the potential possibility of harm or danger, but 'hazard' or 'danger' refers to the harm being proved by scientific facts. Many newspapers and magazines have confused these two concepts, claiming the GM crops are 'severely dangerous' or 'even impact on the offspring' just by surmise, without any supporting scientific data. This really misleads the public, who remains ignorant of the scientific truth.

Second, the terms 'safety' and 'risk' are relative and dynamic concepts. Things considered safe based on today's scientific knowledge may be found to have some unsafe characteristics in the future, while unsafe or harmful things today may become beneficial by eliminating their unsafe properties with the progress of science and new technology. Virtually any human activity may contain risks. Any innovation in science and technology is expected to be a double-edged sword, having both advantages and disadvantages. The most important thing is to balance the benefits and risks of a new technology; i.e. to use the beneficial effects, on one hand, and to avoid the possible risk, on the other. Electrical appliances, automobiles, aeroplanes and vaccinations are not absolutely safe. Electrical appliances can cause electric shock, automobiles result in air pollution, air travel can end in tragedy and vaccinations can result in death, just as certain people are hypersensitive to penicillin. However, these technological advances have never been denied to or abandoned by modern society.

The scientific risk assessment of GM crops includes two main aspects: environmental safety and food/feed safety. In the international debate, a most important aspect commonly ignored is analysis of the risks when biotechnology R&D is forbidden or postponed. This is particularly important for developing or less-developed countries for which the biggest risk is sit idle and do nothing, missing the opportunities offered by the new green revolution.

Analysis of cases

There are several major cases in the debate on the safety of GM crops. Five such cases are now reviewed.

Pusztai's issue

In autumn 1998, Dr Pusztai of the Rowett Research Institute, UK, claimed on a BBC television programme that rats fed a diet containing GM potatoes expressing the *lectin* gene of snowdrop (*gna*) lost body and organ weight and had damage to their immune system. This was the first affair that resulted in an international debate on the food safety of GM crops. Anti-biotechnology organizations, such as Greenpeace and Friends of the Earth, have called this potato a 'killer'. Since then, activists have taken different measures against GM crops, e.g. burning or destroying GM crops in experimental fields and preventing import or export of GM products. Because of the controversy, The Royal Society organized a detailed peer review of all available data related to the work and published a scientific report on the issue in May 1999. In summary, it pointed out that Dr Pusztai's conclusion was wrong in many ways, because of: poor experimental design; lack of 'blind' measurements; uncertainty about the differences in chemical composition of non-GM and GM potatoes; no supplement of proteins in the diet of rats fed with transgenic potatoes; small number of rats and non-standard diet used in the experiment; and inappropriate statistical methods used in data analysis. All of these caused biased results with no consistency (The Royal Society, 1999).

Bt corn and monarch butterflies

In its issue of 20 May 1999, the journal *Nature* reported a study conducted by scientists at Cornell University asserting a negative impact of milkweed dusted with Bt corn pollen on the growth and survival of a non-target insect, the monarch butterfly (Losey *et al.*, 1999). Only 56% of the larvae survived after four days of feeding on leaves dusted with Bt pollen. A debate arose on the environmental safety of GM crops. In fact, the study was conducted in the laboratory, and not under natural conditions. Furthermore, it did not provide data on the number of pollen grains used. To date, some scientific conclusions can be drawn about this incident (Food and

AgBiotech, 2000; Shelton *et al.*, 2001). First, corn pollen is relatively large and heavy; it could not disperse over a long distance. The average amount of pollen found on milkweed leaves 5 m from the cornfield was just 1 grain per square centimetre. Second, new information has been presented from field studies conducted in Maryland and Iowa, USA and Ontario, Canada with the GM corn lines MON810 and Bt 11 since 2000. This indicated that naturally deposited pollen grains from these two corn lines have not seriously affected the growth and survival of monarch butterfly larvae. Laboratory bioassays with Bt pollen density 10 times higher than that typically found inside cornfields showed no significant effects on this non-target insect (Hellmich *et al.*, 2001; Oberhauser *et al.*, 2001; Pleasants *et al.*, 2001; Sears *et al.*, 2001; Stanley-Horn *et al.*, 2001; Zangerl *et al.*, 2001). The real reason leading to the reduction of monarch butterfly populations was the overuse of pesticides and damage to the ecological environment in Mexico.

'Super weeds' in Canada

Some individual volunteer canola plants resistant to three herbicides, so-called 'super weeds', were found in a field in northern Alberta, Canada, caused by transgene flow (MacArthur, 2000). In fact, spraying with 2,4-dichlorophenoxyacetic acid would kill the triple-resistant canola volunteers (Thomas, 2001). It should be stressed that 'super weeds' is not a scientific term but a visualized figuration. There is no evidence indicating the existence of 'super weeds' in nature. In terms of gene flow, it is not specific to transgenic plants, but is a well-known natural phenomenon and a driving force for evolution. There would be no such variation of plant species in nature without gene flow. For example, wheat contains three genomes (A, B and D), which evolved by gene flow among three wild species containing the A, B or D genome. In this regard, transgene flow is not a right reason to oppose or forbid the release of GM crops. The real concerns of transgene flow are the consequences or impacts on the environment rather than gene flow itself, e.g. whether the transgene flow will increase the competitiveness, weediness or invasiveness of a given recipient species. Even when a weed resistant to multiple herbicides occurs, it may still be controlled by new and safe herbicides further invented by mankind, which reflects the real history of science and technology development. In the case of rapeseed, based on its reproductive biology, studies should be intensified on the consequences of gene flow from GM canola to other sexually compatible species, because of the relatively higher cross-compatibility, wind/insect-mediated pollination, long distance of pollen dispersal and the wide natural existence of sexually compatible relatives and wild species, including weeds.

Mexico maize

In November 2001, two scientists from the University of California, Berkeley, published a paper in *Nature* claiming that DNA sequences similar to the CaMV35S promoter and *adh1* gene used in Novartis GM corn Bt 11 were found in samples of maize landraces collected from Oaxaca, Mexico (Quist and Chapela, 2001). Greenpeace called it 'gene pollution' or 'gene contamination', and since then have widely disseminated the allegation that Mexican maize landraces or even the maize gene bank in CIMMYT (International Maize and Wheat Improvement Center) have been 'contaminated'. However, many scientists have criticized this paper, pointing out many mistakes in the experimental methods used. The presence of the *CaMV35S* promoter sequence has been verified to be a false positive (Kaplinsky *et al.*, 2002). The statement of identification of the *adh1* gene in landraces from transgenic maize is totally wrong. The known *adh1* gene sequences in Bt 11 are from the second intron (~180 bp) and the sixth intron (~471 bp) of maize *adh1-1S* gene (the exact sequences used including the exon flanking sequence are identified in US Patent 6,114,608 and are based on the sequence information in GenBank accession X04049 for *adh1-1S*). The PCR sequence reported by the authors in *Nature* was a match to part of a relatively large (160 and 480 bp) sequence of the maize *adh1-F* gene (GenBank accession AF123535) (Irvin, 2002). Apparently, neither the authors nor the editors of *Nature* had checked if the PCR-amplified sequence was similar to the known *adh1-S* gene in Bt 11 but just made the claim based on the mere presence of the word '*adh1*'. Later, the Editor of *Nature* (2002) stated that 'the evidence available is not sufficient to justify the publication of the original paper'. Meanwhile, a statement released by CIMMYT indicated that CIMMYT specialists had screened 152 Mexican landraces and failed to detect the presence of the 35S promoter (CIMMYT, 2002).

It is unfortunate that Greenpeace never considered these scientific data. Certainly, gene flow from GM maize to non-GM maize may occur as in the case of gene flow between non-GM maize cultivars; therefore, it could not be dramatized as 'gene pollution' and taken as the reason to ban GM crops. The right way to reduce risks of gene flow and outcrossing rate based on scientific data is to consider the distribution of landraces and the wild relatives, teosinte, and their sexual compatibility to maize cultivars by dividing Mexico into different geographical zones (D0–D5: D0, no wild relatives in the area under consideration; D1, no compatible wild relatives in the area under consideration; D2, no records of spontaneous hybrids in the area under consideration; D3, occasional natural hybridization, no backcrosses observed in the area under consideration; D4, natural hybridization occurs, hybrids are fertile and backcrosses may occur; D5, natural hybridization occurs fairly often, hybrids are fertile and backcrosses occur frequently); then the environmental impact of GM maize could be evaluated accurately (Custers, 2001).

Chinese Bt cotton

On 3 June 2002, the Nanjing Institute of Environmental Sciences and Greenpeace co-sponsored a meeting in Beijing. As an adviser of Greenpeace, Xue Dayuan from Nanjing Institute of Environmental Sciences released a report entitled 'A summary of research on the environmental impact of Bt cotton in China' during the meeting. On 4 June, an article entitled 'GM cotton damage environment' was published in *China Daily*. On the same day, Greenpeace released the English version of Xue's 26-page report on their website (Xue, 2002). It immediately attracted a huge reaction from Europe and America, and aroused again an international debate on the biosafety of GM crops. In an article published in Germany's agriculture newspaper the next day (5 June), the title had been upgraded to 'Chinese research: large environment damage by Bt cotton'. Ping Lo Sze, Greenpeace's China Program Manager, claimed that 'as farmers growing this GM crop are now finding themselves entangled in Bt-resistant super bugs [once more a term – 'super bugs' – was created by Greenpeace without any scientific basis] . . . transgenic insect-resistant cotton did not deal with any of these problems but caused more problems . . . farmers need to keep spraying chemical pesticides to deal with the increasingly uncontrollable situation' (Greenpeace, 2002). The fact is that transgenic insect-resistant cotton has been commercialized in China since 1997 and been widely accepted by cotton growers. Scientists from China, the USA, Germany, Canada, Belgium, India and other countries have started to comment on and refute Greenpeace's viewpoints.

There were six main conclusions in Xue's report.

1. 'A significant reduction of the parasitic natural enemies of cotton bollworm'. It should be pointed out that this was just the result from laboratory tests and did not reflect the real situation in the field. Even when we use chemical pesticides to kill cotton bollworm, they result in the reduction of parasitic natural enemies too. Thus this is not the fault of Bt cotton itself.
2. 'An increase of secondary pests: for example, cotton aphids, spider mites, plant bugs and other pests had replaced the cotton bollworm as primary pests in some of the cotton fields'. This is in conflict with general biological knowledge. Chemical pesticides are also known to be selective, by which a reduction in population size of target pests would increase the amount of other pests. Insect-resistant Bt cotton does not mean non-pest cotton. Bt insecticidal proteins in the insect-resistant cotton just kill certain pests of Lepidopteran species, but do not kill all kinds of pests including cotton aphids, spider mites, plant bugs and others. Farmers could effectively control those pests by appropriate measures such as spraying of synthetic pyrethroids and organophosphates (Jia *et al*., 2001). The so-called 'super bugs' do not exist in nature at all. Therefore, it could not be deemed that 'GM cotton damaged the environment'!

It must be emphasized that Greenpeace has never quoted positive results but focuses on negative results. Results from the Institute of Plant Protection, Chinese Academy of Agricultural Sciences indicated that the population density of cotton aphids in Bt cotton fields had been reduced by 443- to 1546-fold compared with insecticide-treated non-Bt cotton fields. This was due to a dramatic increase of predator enemies resulting from a 70–80% reduction of insecticide use (Jia *et al*., 2001). Greenpeace did not mention these positive results.

3. 'Stability of the insect community in Bt cotton fields may be less than that in conventional cotton fields, thus the possibility of outbreaks of certain pests in Bt cotton is much higher'. This is pure surmise without any scientific data to support the conclusion. In fact, arthropod biodiversity in Bt cotton fields has been increased compared with that in conventional cotton fields (Wu *et al*., 2002a, 2003).
4. 'Both laboratory tests and field monitoring had verified that cotton bollworm developed resistance to Bt cotton'. To a certain extent, it is true that bollworm resistant to Bt cotton would be created after multiple generations of selection in the laboratory (Jia *et al*., 2001). However, according to field monitoring data, the bollworm populations sampled from different cotton-growing regions during a 5-year study were still susceptible to Cry1Ac protein, and no resistance development has been found (Wu *et al*., 2002b, 2002c). Supported by the '863 High-Tech Program', more than 20 bollworm populations were collected from 23 sites in five cotton-growing regions in China and assayed for their resistance to Bt cotton; no bollworm populations developed resistance to Bt cotton (Jia *et al*., 2001; Wu *et al*., 2002b, 2002c). This baseline information is very important to the monitoring and management of resistance development in cotton bollworm. Insects may develop resistance to any

insecticide including Bt preparations; it is necessary to have successive monitoring and an integrated pest management system in the long term. Proper management can delay the development of insect resistance.

5. 'The resistance of Bt cotton to bollworm decreases over time, farmers must use chemicals 2–3 times to control bollworm'. It is true that the Bt protein content of transgenic cotton in the later stage of development is lowered and thus farmers should spray pesticide once or twice to control the bollworm. However, if Bt cotton is not planted, farmers must spray pesticides 15–20 times during the whole growing season; thus more chemical pesticides would be used to control bollworm.

6. High-dosage Bt protein expression and refugia strategy are commonly used in insect resistance management throughout the world. Xue doubted the actual worth of the application of these two strategies. He claimed that 'there were no effective measures yet to postpone the resistance development or to solve the resistance problem'. Certainly we do agree that it is impossible to completely eliminate the development of resistance; however, it is absolutely possible to delay it. In the northern cotton-growing region of China, the multiple-cropping system actually provided large natural refugia to the bollworm. Investigations indicated that 70% of the fourth generation of bollworm had been raised in cornfields. Chinese researchers have evaluated the function of natural refugia and proposed a low-risk cropping system (Wu *et al.*, 2002b). Entomologists have investigated the migration behaviour of bollworm using a radar detection system, by which it was found that the bollworm migrated to the north-east (no cotton grown in this area) in the summer and returned to the south in the autumn (Wu *et al.*, 2001). Therefore, even though Bt-resistant individuals may appear, the offspring derived from crossing resistant insect individuals with susceptible ones will still be susceptible to Bt, since it is known that the resistance is under the control of a pair of incomplete recessive alleles. In addition, Chinese scientists have demonstrated that GM cotton with double genes could delay the evolution of resistance in bollworm. After 17 generations of selection of bollworm fed on leaves of transgenic tobacco containing either the single *Bt* gene or *Bt/CpTI* double genes, the resistance index in the former case had increased 13 times, while it increased just three times in the transgenic tobacco with *Bt/CpTI* double genes (Jia *et al.*, 2001).

The well-recognized greatest environmental benefit of Bt cotton is not only the 70–80% reduction in use of chemical pesticides, but also the reduction in the rate of harmful accidents to humans and animals caused by the overuse of pesticides. In Greenpeace's report, no allusion was made to these positive results. In China, the annual usage of pesticides in cotton cultivation comprises 25% of the total chemical pesticides used. According to a survey in Shandong province in 2000, pesticide use had been reduced by 15×10^5 kg due to planting of 70,000 ha of Bt cotton (Jia *et al.*, 2001). We do not understand why such a great environmental benefit has not been cited in Greenpeace's report.

Broadly, the international comments on Greenpeace's report were: the article was not passed through peer review; the methodology used was not mentioned in the article; no biological statistical data were provided; there was a conflict with general biological knowledge; and finally it just quoted data according to the authors' personal desire.

The nature of debates

The nature of international debates on the biosafety of GM crops is not a pure scientific issue; rather it is related to economic and trade considerations. In fact, nowadays the biosafety of GM crops has been used as a technological barrier in international trade.

The debate should be based on the scientific criteria. At present, no environmental or food safety issues have been associated with the GM crops authorized for use in commercialization. The long-term impact of GM crops on the environment, food and feed must be monitored, including unintended effects. But the analysis of unintended effects must be associated with the risk, if any, since many changes may occur after transformation. The same is also true for traditional crossbreeding, particularly in wide crossings where unexpected effects may appear. The most effective way to reduce unintended effects is to select superior individuals out of a large population of transgenic plants.

In general, the debates with activists boil down to the issue of whether we need GM crops and its products, and whether we need the progress of science and civil society. The aim of activists is to ban any development in biotechnology, while our aim is to accelerate the development of biotechnology under the conditions of ensuring safety of the environment and human health. This is the ultimate difference between the two sides.

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