

Critical Review

Are Genetically Modified Plants Useful and Safe?

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Summary

So far, plants have been genetically modified essentially to achieve resistance to herbicides, or to pathogens (mainly insects, or viruses), but resistance to abiotic stresses (such as cold, heat, drought, or salt) is also being studied. Genetically modified (GM) plants with improved nutritional qualities have more recently been developed, such as plants containing higher proportions of unsaturated fatty acids (omega-3 and omega-6) in their oil (to prevent cardio-vascular diseases), or containing β -carotene as in the golden rice (to prevent vitamin A deficiency). Possible risks for human health (such as the production of allergenic proteins), or for the environment (such as the appearance of superweeds as a result from gene flow), should be carefully studied, and a science-based assessment of benefits vs. risks should be made on a case by case basis, both for GM plants and for plants obtained by conventional breeding methods.

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Applications of genetic engineering to medicine, which have allowed the production of a number of proteins of therapeutic importance (such as insulin, growth hormone, plasminogen activator, antihemophilic factors, etc.) in large amounts and without contamination by viruses or prions, have generally been well accepted. This is not always the case, at least in some countries, for the applications of genetic engineering to agronomy.

Genetically modified plants (GM plants) or transgenic plants are usually obtained either by direct gene transfer (with the help of electroporation, or of a particle gun), or using as a vector a disarmed Ti (Tumor inducing) plasmid whose

oncogenes (which in nature are transferred from the plasmid DNA to the plant genome and cause plant tumors) are replaced by the gene(s) of interest. The gene(s) become integrated into the plant genome, replicate along with it and are expressed in the recipient plant cells. As it is possible from a single plant cell (a protoplast) to regenerate a complete plant, it is relatively easy to obtain, starting from a single transformed cell, a GM plant which possesses the transgene(s) in all its cells.

Although most GM plants have had additional genes introduced in their genome, some plants have been modified so that one (or several) of their genes is (are) no longer expressed. Among the first GM plants developed, one can mention tomatoes in which the expression of the gene coding for polygalacturonase was blocked using the antisense strategy, thus delaying the hydrolysis of polygalacturonic acids which are constituents of the cell walls, thereby preventing early softening and rotting of these tomatoes, and therefore prolonging their shelf life. Antisense strategy or gene silencing can be used to block mRNA translation or to cause its degradation, thus preventing the synthesis of the corresponding protein. Another example of this strategy consists in preventing the synthesis of an enzyme involved in lignin biosynthesis in order to decrease the lignin content, either in a forage crop to increase its digestibility by cattle, or in wood where lignin is a contaminant difficult to eliminate during the purification of cellulose for the paper industry.

So far, most of the GM plants obtained are herbicide-resistant plants. A herbicide is a substance toxic for plants, but not for animals or man which do not have the target enzyme or the target pathway (such as photosynthesis, or biosynthesis of the essential aromatic amino acids). To kill the competing weeds (which are depleting yields), but not the crop plant with a non-selective herbicide (such as glyphosate), two main strategies can be used: It is possible to protect the crop plant by introducing either the gene coding for a detoxifying enzyme (which degrades, or inactivates the herbicide), or the gene coding for a resistant form of the target enzyme (so that the target reaction will continue to take place in the crop plant).

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Using herbicide-resistant (or herbicide-tolerant) plants such as soybean or canola, can reduce the need for tillage, so that leaves, stems, etc. remain on the soil surface and this can significantly decrease soil erosion.

Plants can be attacked by many pathogens, such as viruses, bacteria, fungi, nematodes, insects. Depending on the plant, the region of the world, the climate, etc., important losses in crop yields can be caused by plant pathogens. Farmers are usually trying to protect their crops by using pesticides, which are chemicals often also toxic for man and the environment and which can persist in the soil and the rivers or lakes for long periods. But now insect-resistant plants (maize, soybean, cotton, etc.) have been obtained by introducing into the plant genome the gene of a bacterium (*Bacillus thuringiensis* or Bt) coding for a protein (called Bt protein) which is toxic for insects (for instance insects which attack maize, rice, cotton, etc. and can cause important yield losses), but not for man or animals, so that the plant itself produces the insecticide protein, and there is no need to grow the bacteria, extract and purify the protein and deliver it to the fields. It should be mentioned that the bacterium producing this protein has been used in suspension as a pesticide for over 40 years, even by organic farmers. In addition it has been observed that the insect-resistant GM plants, because they are not attacked by insect larvae, do not have wounds which facilitate infection by fungi, and are therefore less contaminated by mycotoxins (such as aflatoxin, for instance) which can cause very serious liver diseases (including cancer) in man. Bt plants are resistant to some insects, not to all insects, but smaller amounts of chemical insecticides can then be used, decreasing the pollution, the costs (and the risks) for the farmer, while reducing the yield losses.

Plants can be protected from infection by viruses upon transformation with a gene coding for a viral protein, such as the coat protein. An interesting application of this strategy is the development of virus-resistant papaya which have been obtained upon introduction into papaya of the coat protein gene of the Papaya Ringspot Virus, allowing the control of this virus in Hawai.

Whereas crop production should be increased in order to feed an expanding world population, land areas available for agriculture are decreasing because of erosion, urbanization, desertification, soil pollution, etc., so that it is an important goal to obtain plants able to grow either in usually unfavorable climate conditions, or on soils presently not suitable for agriculture. Therefore many efforts are being made to identify in non-crop plants genes conferring resistance to abiotic stresses (heat, cold, drought, salt, etc.) and transfer these genes into crop plants.

A sustainable agriculture requires solutions to problems such as chemical dependence (because, as already mentioned, the chemicals used are often toxic to man and the environment), pests, drought, high salinity, etc. and conventional methods are not likely to provide the necessary solutions.

In addition to the development of plants resistant to herbicides, pathogens, or abiotic stresses, efforts are being made to obtain plants with improved nutritional qualities (sometimes called 'second generation GM plants'. Among those, one can mention plants with a higher content in essential amino acids (such as lysine, methionine, etc.) of their seed storage proteins (which is important for populations eating little or no meat), or plants with a higher proportion of unsaturated fatty acids (such as omega-3 and omega-6) in their oil (this is important in the prevention of cardio-vascular diseases) which can be achieved by the introduction of genes coding for desaturases, under the control of a seed-specific promoter in order to trigger their expression only in seeds. In golden rice, two genes coding for enzymes necessary to produce β -carotene (a precursor of vitamin A in man) have been introduced in order to fight vitamin A deficiency, which causes very serious problems (including blindness, and even death) to hundreds of millions of people eating almost exclusively rice, essentially in the third world. Genes improving iron uptake have also been introduced into golden rice, so that this rice also helps prevent anemia.

Another interesting development, called molecular farming (or pharming) consists in the cultivation on a large scale of transgenic plants producing substances of therapeutic importance, such as vaccines (especially edible vaccines), or antibodies, in large amounts, at low costs, and without contamination by human pathogens such as viruses or prions. GM plants can also be used to make biodegradable plastics (rather than using petroleum), or to accumulate heavy metals which are polluting the soils (a method called phytoremediation).

In 2003 there has been a 15% increase (+ approximately 9 million hectares) and in 2004 a further 20% increase (+ approximately 13 million hectares) in the surfaces used worldwide to grow GM plants, so that in 2004 about 5% of the 1.5 billion hectares of all global cultivated cropland, namely about 81 million hectares (approx. 200 million acres) was occupied by GM crops (mainly soybean, cotton and maize). The genes introduced are conferring essentially resistance to herbicides (75%), to insects (17%), or to both (8%). But why, as mentioned in the introduction, are GM plants not always well accepted by public opinion? Do they present risks, either for human health, or for our environment?

First, one should remember that plants (and other organisms) have naturally been genetically modified throughout evolution. Introducing one or several new gene(s) into a plant genome using genetic engineering methods is not fundamentally different from what nature has been doing, or from what man has been doing by plant breeding and selection. Then, it is not possible to say *a priori* that the methods used in genetic engineering and the resulting GM plants are either good or bad. One should judge on a case by case basis, depending on the benefits for the farmer, or the

consumer, or the population in general, and on the possible risks for human health or for our environment, for instance.

As far as human health is concerned, it should be stressed that so far no adverse effect of GM plants has been documented, although the first GMOs were created about 30 years ago and millions of people have been eating GM plants or products derived from GM plants. Eating foreign DNA and protein cannot be considered as a health hazard, as everything we have been eating throughout our entire evolution contain foreign DNA and protein. But some of the chemicals (such as pesticide residues) which we are ingesting when we eat pesticide-treated plants or products derived from these plants, are quite toxic, or even carcinogenic. Growing GM plants producing a biodegradable insecticide protein (such as the Bt protein) can significantly reduce the amounts of chemical pesticides used by the farmers.

Among the risks which have been mentioned, there is the possibility that antibiotic-resistant bacterial strains might appear. Although antibiotic resistance of bacterial strains which are pathogens for man is a real problem, it is mainly caused by misuse of antibiotics in human and veterinary medicine, and it is not a simple mechanism for an antibiotic resistance gene to get transferred from a GM plant to a soil bacterium and then to a bacterium pathogenic for man. However this possibility has been seriously considered, since an antibiotic-resistance gene was generally linked to the gene of interest to be transferred into the plant genome, in order to serve as a marker in the selection of transformed cells (grown on a medium containing this antibiotic) because the efficiency of the transformation techniques is usually low. But there are now methods available to eliminate the marker gene, and other selection methods are now being developed (such as growth on mannose, an unusual sugar, that only transformed cells can metabolize, as they have received as a marker a gene coding for an enzyme catalyzing mannose metabolism).

Some people fear that GM plants, or food products derived from them, may cause allergies. But non-GM plants, either wild species or crop plants obtained by conventional breeding (for instance the kiwi fruit), can also contain proteins to which a certain percentage of individuals are allergic. In fact it is difficult to predict whether a new protein will be allergenic on the basis of its amino acid sequence or its conformation, even when comparing it to known allergens, so that the allergenic potential has to be studied for each plant, whether obtained by conventional breeding or gene transfer technology. On the other hand, genetic engineering methods (gene silencing for example) can be used to block the synthesis of an allergenic protein in a plant, thus resulting in a GM plant which is not allergenic, or less allergenic than the initial plant obtained by conventional breeding.

Among possible risks concerning the environment, gene flow is often mentioned. The pollen of a GM plant could

pollinate the flowers of a non-GM plant (of the same species) grown in an adjacent field. Or a herbicide-resistance gene could be transmitted by pollen from a cultivated GM plant to weeds of the same family, which could thus become resistant to this herbicide (and become 'superweeds'). New herbicides would then have to be developed, as in the case of the fight against antibiotic-resistant pathogenic bacteria which requires the use of new antibiotics. This risk has to be evaluated on a case by case basis: In some cases, for example in the case of maize in Europe, there are no other plants of the same family in the environment, or in the case of vine the root-stock (transformed to be virus-resistant) does not flower and therefore does not produce pollen. Generally speaking, pollen dissemination depends on a number of factors such as the size and weight of the pollen grains, the strength of the winds, etc. and this should be carefully studied, hence the importance of field trials, which ironically are sometimes destroyed by those who are asking for more experiments before GM plants are released.

Gene flow can be prevented (or controlled) by physical containment (but as it is sometimes leaky, escapes can propagate), or by using male sterile lines, or by putting the transgene under the control of a chemically induced promoter, or by using a split gene which requires trans-splicing, or integrating the transgene into the DNA of chloroplasts rather than into the DNA of the nucleus (as pollen grains do not contain chloroplasts). Mitigation techniques have recently been proposed, consisting in flanking the transgene (i.e., Bt gene, or herbicide-resistance gene) with mitigator genes which are good for the crop, but bad for the weed, resulting in a disadvantaged weed: among the genes which can be used for mitigation, genes for dwarfism, or anti-shattering genes, can turn a weed into a non-competitive weed.

Another potential risk for the environment which is sometimes mentioned is the appearance of insect strains resistant to the insecticide produced by the transgenic plant. It has been proposed to provide, next to the fields of GM plants, refuges containing untransformed plants, on which insects can feed without being under a selection pressure that might lead to the appearance of a resistance.

In conclusion, it is clear that gene transfer technologies can have very important applications, not only in medicine, but also in agriculture, for instance to decrease losses due to plant pathogens while reducing the use of chemical pesticides polluting the environment, or to generate plants able to grow in usually unfavorable climatic conditions or on soils presently unsuitable for agriculture, or to obtain plants with improved nutritional qualities (such as golden rice, to name just one example). Other GM plants can be developed for molecular farming to produce at low cost large amounts of substances of therapeutic value without human pathogens.

As far as biosafety is concerned, it should be remembered that all methods used for plant breeding, including self- and

cross-pollination, generation of hybrids, mutation (with X-rays or chemicals), protoplast fusion, tissue culture (which causes somaclonal variations, namely chromosomal instability of embryogenic plants regenerated from tissue culture), as well as recombinant DNA techniques, can generate unanticipated effects in plants. All these methods can result in the appearance of a new toxic substance, or of a new protein which will turn out to be allergenic for a certain proportion of the human population. Conventional breeding has generated toxic plants, for instance a potato containing high levels of toxic solanin, or a celery containing high levels of carcinogenic psoralen, so that these plants had to be removed from cultivation. GM crops and derived foodstuffs are presently being rigorously tested, but this should also be done for conventional ones which can contain not only allergens, but also poisonous proteins or other toxic substances.

As far as our environment is concerned, populations of all organisms are made of mutants, and genetic exchange between different organisms is a natural event which has been taking place throughout evolution. Gene flow could have undesirable consequences, for instance if it results in the appearance of a superweed, but different methods can be used to limit gene flow, or to generate a disadvantaged weed rather than a superweed.

Research is therefore necessary and should be continued, but a science-based assessment of benefit vs. risks should be made, and GM plants, as well as plants obtained by conventional breeding, should be rigorously tested. The results of this research should be communicated to the public, in order to allow rational discussions and eventually public acceptance of the best solutions to the global problems which sustainable agriculture is facing.