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# The Importance of Genetic Modification for Contents of Bioactive Compounds in Feed and Food Plants

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## Abstract

Plant breeding has been of immense importance to human beings throughout history. The present human population could not have been fed without the many fold increases in crop yields that plant breeding has provided. Over the last decade, genetically modified crops have become accepted by many countries, provided that they are subjected to thorough safety assessment and authorization on a case by case basis. There are risks associated with plant breeding. The novel trait found in any new variety, independent of the breeding technique involved, will have its basis in genetic alternations. In addition to these traits specific genetic alternations, there may be additional genetic alternations. Some of those alterations, which may not be related to the new trait of the breed, may cause adverse effects such as production of bioactive compounds with toxic effects. Some adverse effects may be discovered while others remain unknown. The risks associated with genetic modification may be higher than for some traditional breeding technologies but at same time risks may be lower than that of some other traditional breeding technologies. Despite this, Genetic Modification Organisms are often understood as inherently risky until their safety is proven through a rigors safety assessment and authorization procedure, while at the same time crops generated using traditional technologies are considered safe and no documentation or authorization is needed. While the first Genetic Modification Organisms were developed with agronomical traits, such as pest resistance and pesticide tolerance, new generations enhance the level of nutrients or reduce the level of toxicants naturally found in plants. Genetic modification represents a new and powerful tool for plant breeding. The global community has decided to progress with precaution to limit the risk of adverse effects while at the same time harvest the benefits.

## Introduction

Plant breeding still has an immense importance to human good fortune. The current population could not have been fed without the many fold increases in crop yields that plant breeding has provided. However, new breeding techniques, such as genetic modification, may provide a more effective way of breeding but are at the same time associated with risks. Here, focused how genetic modification involved in breeding techniques. Such as

A. Comparison between traditional plant breeding and genetic modification,

B. Genetic modification may remove harmful bioactive compounds from food and feed,

C. Genetic modification may add beneficial bioactive compounds in food and feed.

## (A) Comparison between traditional plant breeding and genetic modification

Genetic Modified Organism (GMO) crops were introduced to the market in 1996. Since then the global area planted with GMO crops has increased rapidly (see Figure 1). In the USA, there have been issued in the order 13 000 permits for field trials, and in the order of 100 GMOs have been deregulated for commercialization. Since the beginning of the last century, plant breeders have hybridized different plant materials in order to create new variation on which selection can be imposed. Crossing can be done within a species or between more or less related species. Some species hybridize in nature, while others can only be crossed using special techniques. Embryo rescue was used to obtain a cross between different species as early as in the 1920-ies. The protoplast fusion technique was developed from the 1970-ies. Crossing of a crop species with a related, non- domesticated species is done in order to introduce genes/alleles not present in the gene pool of the crop species.

In Figure 1, Global area of GMO crops. Reprinted with permission from the Global Status of Commercialized Biotech/GM Crops, International Service for the Acquisition of Agro-biotech Applications [1]. By exposing plant material to chemical mutagens or ionizing radiation, the mutation rate can be increased dramatically above the natural background mutation rate. Proof of Mendelian inheritance of changes induced by X-rays was presented in the late 1920-ies, but induced mutagenesis did not come into practical plant breeding until the 1950-ies. Induced mutations include both mutations in genes and chromosomal rearrangements. In the IAEA Mutant Variety Database (http://www-mvd.iaea.org, accessed 12.01.09) 2385 released varieties developed through mutagenesis are listed. Around 90 % of the varieties have been mutated using radiation. Recent analyses of induced mutant populations using the TILLING technique indicate a mutation rate of 5000-50000 per cell [2].

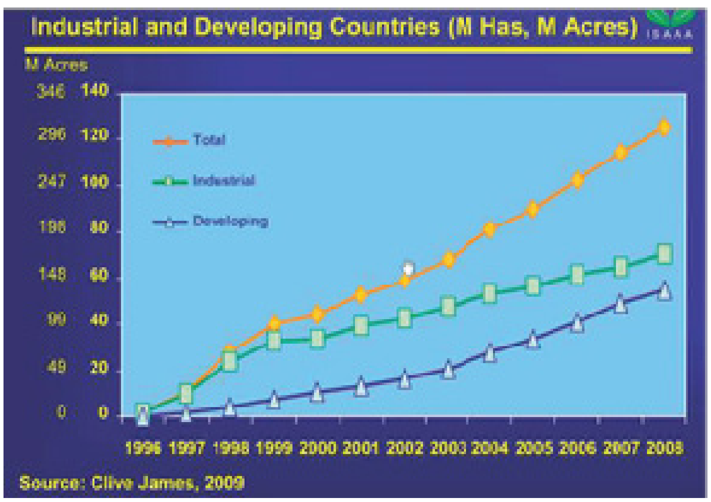


*Figure 1: Amplification plots of PLP, SRY, and PAR genes.*

A genetically modified organism (GMO) is an organism whose genetic material has been altered using genetic engineering techniques. These techniques, generally known as recombinant DNA technology, use DNA molecules from different sources, which are combined into a genetic cassette containing a new set of genes. This DNA cassette is then transferred into an organism, giving it a set of modified or novel genes. Transgenic organisms, a subset of GMOs, are organisms which have inserted DNA that originated in a different species.

Cisgenic GMOs do not contain genes from other species but have inserted a new genetic combination of their own genome. All the techniques described above introduce genetic variability and new genetic materials. The current use of the term genetically modified organism (GMO) is therefore misleading. All new plant varieties are genetically altered through the breeding process. Genetic modification is one out of many techniques that introduced genetic alterations. Independent of the specific technique used to introduce genetic variability the pool of variants go through a process of selection. In this process the variants with the superior genetic properties is selected. However, selection for one trait may lead to correlated effects on other traits such as bioactive compounds. This may occur when one gene affects several traits or it may occur due to effects of closely linked genes. Disease and pest resistance is often based on the production of certain enzymes or secondary metabolites that are toxic to plant pathogens or insects. These substances are sometimes toxic to human beings as well, in which case selection for resistance may lead to adverse effects to human health.

A number of genes closely linked to the genes encoding the desired trait are likely to be co-introduced into any new variety descending from crossing or hybridization. In most cases the identity and function of these genes will be completely unknown. Unlike introduction of new alleles/genes by crossing, introduction by transformation does not involve the linkage drag described above and thus there will be no unintended introduction of irrelevant genes linked to the gene of interest.

The food safety of plants genetically altered through plant breeding was not questioned until transgenic crop plants came into commercial production in the 1990-ies. A large number of food crop varieties cultivated during the last century were developed using induced mutagenesis or introgression of genes from related species. There are not many examples of food crops with an adverse effect on human health that is due to breeding and not to characteristics intrinsically present in the species. This may indicate that there is not a strong need for safety assessment of foods derived from crop varieties developed through these techniques. However, subtle or long-term adverse effects of genetically altered plants or traditional varieties may be difficult to detect.

### (B) Genetic modification may constitute a risk for increased content of harmful bioactive compounds

The novel trait found in any new variety, independent of the breeding technique involved, will have its basis in trait specific genetic alternations. Furthermore, in addition to these traits specific genetic alternations there may be more or less of additional genetic alternations. The unintended alternations may be discovered while others remain unknown. Some of the unintended traits may be unwanted due to adverse effects on the plant, the environment or human health.

All breeding material is evaluated throughout the breeding process, and individuals with obvious unfavorable traits are discarded. However, this evaluation has historically focused on the quality of the new plant and especially on the new traits that were the aims of the breeding process. Thus, unintended effects due to the breeding process have not been looked at. The screening is generally limited to easily observable traits, that is, morphological or agronomical traits with known adverse effects. Contents of toxic compounds, allergens and nutrients are sometimes measured in plants were they are known to occur (e.g. glycoalkaloids in potato). However, in general very little safety related research is conducted on non-GMO varieties.

Genetically modified (GM) varieties, which are derived through recombinant DNA technology, are by legislation required to be subject to extensive safety documentation, public safety assessment and regulatory authorization before they are accepted for cultivation or food purposes. The safety assessment is based on European and international guidance documents developed by international bodies such as The European Food Safety Authority (EFSA) and the CODEX ALIMENTARIUS within the United Nations system. Several issues must be thoroughly documented. This includes; how the food crop was developed, the molecular biological data which characterizes the genetic change, composition of the novel food compared to non-modified counterpart foods, nutritional information compared to non-modified counterparts, potential for introducing new toxins, and the potential for causing allergic reactions. The compliance costs for regulatory approval, to ensure health and environmental safety, are 6 to 14 million USD [3].

There are not yet any well documented examples of adverse health effects associated with commercialized GMOs. Regarding non-GMOs there are a limited number of well documented incidents with adverse health effects associated with the breeding [4]. One example of this is selection for pest resistance leading to increased levels of furanocoumarins in celery. Furanocoumarins can cause severe skin irritations in humans and are carcinogenic. Varieties bred for enhanced insect resistance in celery has caused skin problems among workers that handle these plants. Another example is potato and tomato, where selection for disease resistance, or genetic drift, can lead to increased and toxic levels of glycoalkaloids.

There exist, as far as I now, only one report on the comparative safety of various breeding techniques. This is the National Academy of Sciences report from 2004 on approaches to assess unintended health effects in genetically engineered foods [5]. Various breeding techniques are scored along the scale likelihood of unintended effects (Figure 2). Likelihood of unintended effects from different breeding techniques. The GMOs are made from different rDNA techniques associated with different levels of risk. Reprinted with permission from Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects, 2004 © by the National Academy of Sciences, Washington, D.C.

The main finding in this assessment is that there are risks associated with all breeding techniques and that there is no particular high risks associated with GMOs relative to some of the older and so called conventional breeding techniques. Thus, the belief that risks associated with foods derived from GMOs are qualitatively different from risks associated with foods from other crop breeding techniques are not supported by scientific inquiry so far. Indeed, most if not all of the biological mechanisms active when a GMO is generated, are also found to be active to a smaller or greater extent when the other breeding techniques are applied. This is supported by a workshop organized recently by EFSA which in relation to risk assessment recommend the following "The focus on only GM crops defies scientific evidence. In the longer term, risk assessors could develop an alternative approach on a scientific basis."[6].

### (C) Genetic modification may remove harmful bioactive compounds from food and feed

There are at least 35 000 different secondary metabolites produced by plants [7]. Many of these are toxic and play an evolutionary role in the protection against herbivore animals, insects and microorganisms such as nitrogen compounds (alkaloids, cyanogenic glycosides etc.). When considering consumption of food plants with toxicants the margin of safety is small in many cases [8]. The presence of harmful bioactive compounds in plants is not only due to endogenous production but may be produced by microorganisms as well. It has been suggested that toxicological data, as well as structural similarity "should serve as a guide for the removal of the most toxic compound from plant foods" [9]. Genetic modification provides, together with traditional breeding techniques, means to reduce the level of harmful bioactive compounds in food plants, both those caused by plant chemistry and those caused by microorganisms.

### Cyanide

It is estimated that at least 2500 plant taxa produce



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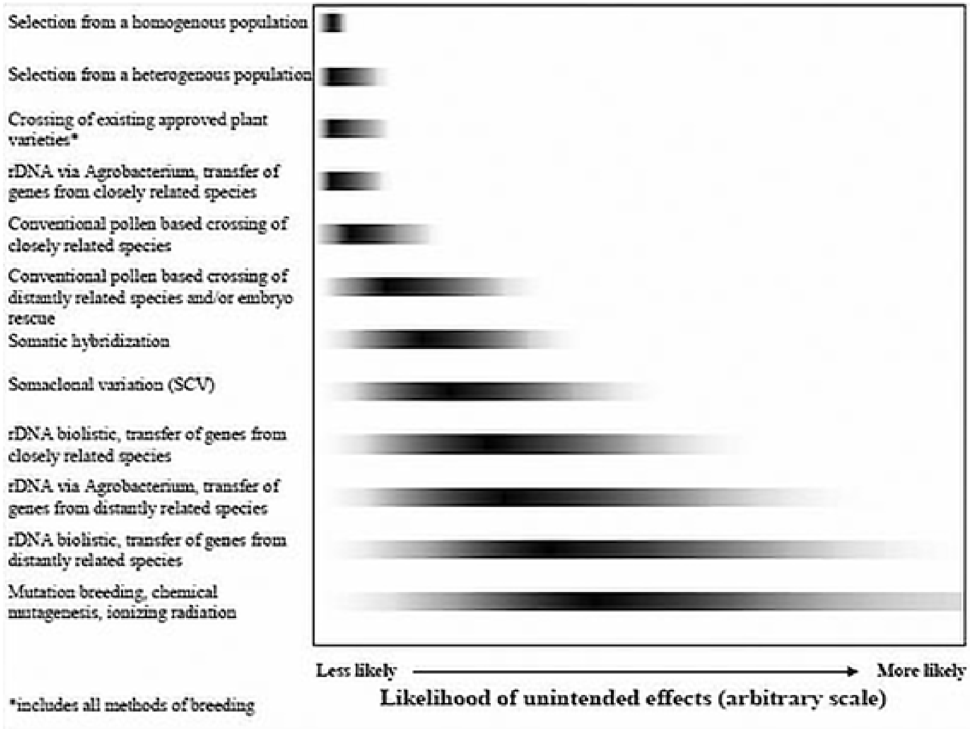


*Figure 2: Melting curves related to amplified products of SRY, PAR, and PLP genes.*

cyanogenic glycosides which are toxic compounds [10]. Among these we find crops such as cassava, sorghum, almond, lima beans and white clover. Bitterness in food from such crops is determined by the content of the toxin [11]. Cassava is the most important root crop in the world. It is the second most important staple crop in Africa and is used extensively for starch production in South East Asia [12]. A major drawback of the cassava crop is a high level of the cyanogenic glycosides, especially linamarin, which generate hydrogen cyanide when the plant tissue is disrupted. When cassava products are used as staple food the toxic compounds are removed by careful processing [13]. Unfortunately, careful processing reduces the nutritional value by the loss of proteins, vitamins, and minerals. Moreover, incomplete processing results in high cyanide exposure and diseases such as tropical ataxic neuropathy after chronic low level exposure and konzo after acute exposure [14].

Traditional plant breeding has generated cultivars with high and with low levels of cyanogenic glycosides but not been able to establish new varieties devoid of these compounds. Using genetic modification several cyanogen-depleted cassavas have now been developed. This has been achieved by RNA inhibition technology to knock down expression of enzymes involved in biosynthesis [12]. Another approach has also proved successful. Here, an enzyme is overexpressed that provides for the volatilizations and removal of the toxin during food processing [15]. Both approaches provide a safer food product.

## Glycoalkaloids

Glycoalkaloids, such as solanine, is a family of steroidal toxic plant metabolites in potato and related species commonly used in potato breeding [16]. The highest levels of glycoalkaloids are found in flowers and leaves, but the levels found in tubers may also be considerable and vary substantially between cultivars [16]. A level of 200 mg glycoalkaloids/mg potato, which is generally accepted as the highest tolerable limit, has a zero safety margin [17]. It is also known that the level of glycoalkaloids in potato tend to increase during storage and after exposure to light. There are cases of food poisoning from consumption of potato. Mild clinical symptoms include abdominal pains, vomiting and diarrhea. Potato related adverse health effects have also been found in experimental studies on human volunteers but are not frequently reported, probably due to a serious underreporting since potato are consumed daily and gastrointestinal disturbances are very common [18]. Deaths caused by potato are rare, but according to Smith et al. [19] “The narrow margin between toxicity and lethality is obviously of concern.”

Several approaches have been exploited by genetic modification to successfully reduce the level of glycoalkaloids in potato. One of those approaches is based on the overexpression of a methyl transferase from the soybean plant. This reduces the level of free cholesterol and glycoalkaloids in the tubers [20]. Several other approaches have achieved reduced levels of toxic glycoalkaloids in the edible tuber by the reduced expression of enzymes involved in glycoalkaloid glycosylation [21]. A recent study was conducted to study changes in the overall metabolite composition in both genetically modified and traditional breed potato tubers. Interestingly, few differences were found between the genetically modified tubers and their parental lines, while different traditional cultivars showed large variations in the metabolite profiles [22].

## Caffeine

Even though caffeine was isolated in the early 1820s, the main biosynthetic pathways were not fully established until recently [23]. The physiological role of purine alkaloids, such as caffeine, has until recently largely been unknown but the main hypothesis is chemical defense. The identification of genes involved in biosynthesis opens the possibility to make naturally decaffeinated coffee or to introduce caffeine as a natural pesticide to protect against herbivores or pathogens in other plants.

Since caffeine may produce adverse effects, such as palpitations, increased blood pressure and sleep disruption, efforts have been made to produce naturally decaffeinated coffee plants. This has not yet been fully achieved but the caffeine level has been reduced up to 70% by introducing RNAi constructs repressing homologous N-methyl transferases [24].

Interestingly, caffeine may be used as a pesticide as well. Tobacco, which does not contain caffeine, has been genetically modified to synthesize caffeine. This has been achieved by introducing a multi-gene vector expressing three N- methyl transferase genes sufficient for caffeine production. This plant was less susceptible to caterpillars. The expression of caffeine was relatively low (<5 ppm) and the protective effect may partially be caused by activation of endogenous defense-related genes and the plant was more resistant to pathogenic bacteria and virus [25].

## Detoxification of Zearalenone

Maize is often contaminated by moulds, including the zearalenone producing Fusarium graminearum. Even though such contamination has been well known for decades, preventive measures are costly and inadequate. Even though zearalenone is a mycotoxin, it is a safety issue in relation to consumption of plants. Recently a GM-maize harbouring a detoxification system was developed. A bacterial gene encoding an alkaline lactonhydrolyase was cloned and used to transform maize. The GM-maize had a substantially lower level of zearalenone and the same approach may be used to remove other problematic mycotoxins [26].

**Genetic modification may add beneficial bioactive compounds in food and feed**

There are serious nutritional and environmental deficiencies associated with the current agriculture and food supply in certain parts of the world. Even though most people obtain sufficient energy from their food there are nutrient deficiencies in major staple crops such as rice and maize. Plant breeding, including genetically modified crops, may undoubtedly contribute to an increased food production as well as to ameliorate some of the nutritional and environmental deficiencies associated with food production today [27]. All the different nutrients found in a food plant may be modified, including proteins and amino acids, oils and fatty acids, carbohydrates, vitamins and minerals, as well as the other thousands of different metabolites. Here, just two examples will be mentioned.

**Vitamin A**

Millions of people die or become victims to chronic diseases due to food deficient of nutrients every year. Vitamin A deficiency is a leading cause of preventable blindness and child mortality and is a public health problem in more than half of all countries. According to the WHO and CDC (Center for Disease Control, USA), 250 million preschool children are vitamin A deficient. Half a million are estimated to become blind every year, of which a majority (70%) dies within one year after becoming blind.

Rice varieties have been developed with sufficient levels of vitamin A to strongly reduce the problem of vitamin A deficiency. By the addition of only two genes, phytogene synthase and phytogene desaturase, the biochemical pathway responsible for ủ-carotene is reconstituted [28]. New varieties could have been on the market within a few years if the increased pro-vitamin A content had been achieved with traditional breeding techniques such as mutagenesis or wide-hybridization. However, since gene technology was a part of the breeding process the regulatory requirements and heavy documentation needs are still not passed.

## Antioxidants

Anthocyanin, which is a class of antioxidant pigments produced by higher plants, have been linked to increased protection against different age related diseases, such as cancers and cardiovascular disease [29]. The levels of anthocyanin vary substantially between different food plants. Attempts have therefore been made to increase the expression of such pigments in major fruit or vegetables.

One recent example is tomato genetically modified to express higher levels of anthocyanin [30]. The plant has been gene modified by the introduction of two transcription factors from snapdragon. The anthocyanin level was found comparable to that of blackberries and blueberries. The antioxidant level increased threefold and both the peel and the flesh of the tomato had intense purple coloration. In a pilot study it was shown that the lifespan of cancer-susceptible mice was significantly extended when fed the new anthocyanin tomato compared to the unmodified tomato.

## Conclusion

Over the last decade GMOs have become accepted by many countries, provided the GMOs are subjected to thorough safety assessment and safety management on a case by case basis. The risks associated with genetic modification may be higher than some, while at the same time smaller than some others, of the traditional breeding technologies. Despite this, GMOs are understood as risky until their safety is proven through a rigors safety assessment and authorization procedure, while food crops generated with other technologies are considered safe and no documentation or authorization is needed. While the first GMOs were developed with agronomical traits, such as pest resistance and pesticide tolerance, new generations enhance the level of nutrients or reduce the level of toxicants naturally found in plants. In future, genetic modification represents a new and powerful tool for plant breeding. The global community has decided to progress with precaution to limit the risk of adverse effects while at the same time harvest the benefits.

## Consent for Publication

We certify this manuscript has not been published elsewhere and is not submitted to another Journal.

## Competing Interests

The author(s) declare that they have no competing interests.


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