Genetically modified foods and allergy

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A B S T R A C T

2015 marked the 25th anniversary of the commercial use and availability of genetically modified crops. The area of planted biotech crops cultivated globally occupies a cumulative two billion hectares, equivalent to twice the land size of China or the United States. Foods derived from genetically modified plants are widely consumed in many countries and genetically modified soybean protein is extensively used in processed foods throughout the industrialised countries. Genetically modified food technology offers a possible solution to meet current and future challenges in food and medicine. Yet there is a strong undercurrent of anxiety that genetically modified foods are unsafe for human consumption, sometimes fuelled by criticisms based on little or no firm evidence. This has resulted in some countries turning away food destined for famine relief because of the perceived health risks of genetically modified foods. The major concerns include their possible allergenicity and toxicity despite the vigorous testing of genetically modified foods prior to marketing approval. It is imperative that scientists engage the public in a constructive evidence-based dialogue to address these concerns. At the same time, improved validated ways to test the safety of new foods should be developed. A post-launch strategy should be established routinely to allay concerns. Mandatory labelling of genetically modified ingredients should be adopted for the sake of transparency. Such ingredient listing and information facilitate tracing and recall if required.

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Introduction

Genetically modified (GM) foods have had their DNA changed by genetic engineering to enhance resistance to pathogens and herbicides and/or to provide better nutritional value. New GM crops are now also being developed for the production of recombinant medicines and industrial products.[1-3] The first GM food in the form of the Flavr Savr late-ripening tomato was marketed unsuccessfully about two decades ago.[4] The research that produced the Flavr Savr tomato was a scientific success but it was a commercial failure. This demonstrated the difficulty of bringing GM products to market; how objections with little or no scientific evidence can influence public opinion and ultimately determine commercial success or failure.[4]

2015 marked the 25th anniversary of the commercialisation of GM crops. In the last two decades the area of biotech crops planted globally has increased at an astonishing rate. A cumulative two billion hectares, equivalent to twice the land size of China or the US, were successfully cultivated globally between 1996 and 2015.[5] Most of the growth has focused on crops in high demand including potato, canola, maize, cotton, soybean, rice, and squash. Foods derived from GM plants are now widely consumed especially in the US but also in other countries, and GM soybean protein is extensively used in processed foods throughout the industrialised world.

Concerns about genetically modified foods

When a new gene is introduced into a plant's genome, a new protein may result that could become an antigen when eaten if it is foreign to a person's normal diet. In 2000, Grace Booth in the US developed anaphylaxis after eating corn tacos. Earlier that year it was discovered that some taco shells contained a pesticidal protein, Cry9C, derived from *Bacillus thuringiensis*. Cry9C was introduced into GM corn to kill several predatory insects and was only ever approved for animal feeding. It entered the human food chain because of cross-pollination when the GM crop was planted too close to normal crops. As other causes of Booth's anaphylaxis could not be determined, Cry9C protein was presumed to be the culprit. The US Centers for Disease Control and Prevention never proved any direct link between Cry9C and development of allergies, but the episode perpetuated the spectre in the minds of the public and media that GM foods cause new allergies.[6]

基因改造食品與過敏

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2015年是基因改造農作物商業化25週年。現今全球用作種植基因改造農作物的耕地達至20億公頃，相當於中國或美國土地面積的兩倍。許多國家已廣泛食用以基因改造植物製成的食品，而工業化國家亦大規模使用基因改造黃豆蛋白來製成加工食品。基因改造食物對現時或將來的世界糧食短缺和藥品製造問題提供了一個解決方案，然而亦引發人們對基因改造食品安全的擔憂，縱然這往往可能是基於很少甚至沒有確實證據的情況下產生。同樣因為健康風險的原因，一些有飢荒問題的國家拒絕接受基因改造食物的援助。儘管基因改造食物進行嚴格評估才批准銷售，人們主要的關注包括這些基因改造食物可能含有過敏原和毒性物質。科學家必須讓人們參與並進行建設性的循證對話以釋除公眾疑慮。與此同時，須開發並改善驗證方法以作新食品的安全性測試，定期制定新食品售賣後的策略以消除公眾疑慮。須推行強制性基因改造成分標籤制度來提高透明度，有需要時此舉亦有助加快食品追蹤和回收。

Opponents of GM technology have suggested that GM foods contribute to the huge increase in food allergies in the US, especially in children.[7,8] This ignores the fact that there are no GM versions of the many foods that commonly cause food allergies, namely eggs, dairy, shellfish, tree nuts, and peanut so the increasing prevalence of these most common food allergies cannot be attributed directly to GM technology.

Despite this logic, critics of the GM food revolution have made a substantial impact to the extent that some nations have rejected much-needed food aid to alleviate famine.[9] In the developing world many millions of people are chronically undernourished and do not have access to sufficient food. Such GM food technology may be able to help solve some of these global challenges.

Safety of genetically modified foods

The World Health Organization stated that it is not possible to make generalisations about the safety of GM foods and this should be assessed on a case-by-case basis.[10] Notwithstanding this statement, GM foods that are available for public consumption have passed detailed risk assessments, including tests for allergenicity. Foods derived from GM technology have been consumed by millions of people across the world without any consistent reports of ill effects. Furthermore, many conventional foods have been produced over centuries through genetic transfer achieved through artificial breeding. Technology has always played a central role in natural food production.[11]

A recent scientific advisory board of the National Academies of Sciences, Engineering, and Medicine found "no substantiated evidence of a difference in risk to human health between commercially available GM crops and conventionally bred crops".[12] The advisory board also discovered no persuasive evidence that GM crops had caused any adverse health effects.

Two major concerns about the safety of GM foods are whether they are allergenic or toxic. Allergenicity may have arisen in several ways. Genetic engineering may have resulted in a new protein, or a known allergen was introduced, or the inherent ability of a GM crop to cause allergies was enhanced.

Two widely reported cases of allergenicity in experiments on GM foods fuelled speculation that they may be responsible in part for the worldwide increase in allergies. The first, in 1966, involved transfer of a Brazil-nut protein into a soybean to enhance the soya bean's nutritional value. An allergenic protein was also transferred and caused an allergic reaction in human volunteers.[13] This food was never approved for the market. The second, in 2005, involved experiments on mice in which a bean engineered to resist pea weevil triggered an immune reaction in the lungs of the animals.[14] These examples are often cited to support claims that GM technology is dangerous and unpredictable. An alternative interpretation is that safety testing was effective in both cases before either product was released onto the market.

Critics of GM food have also claimed that the rise in the number of soybean-allergic subjects in the UK was linked to the development of GM soybean destined for the US market but there was very little exposure to GM soybeans in the UK.[15] More likely the rise in prevalence of soybean allergy in the UK was caused by the greater recent consumption of non-GM soybean.[15]

There is a complex interplay between a person's immune system and a potential allergen. Proteins become allergens when they can bind immunoglobulin E. However, even proteins that can bind immunoglobulin E will only cause allergies if the person has a corresponding sensitivity. The more readily GM foods become available, the more people may be exposed to new proteins. Although there is potential for new sensitivities to develop, this is not a foregone conclusion. In addition, GM foods do not always contain a new protein, for example, when some genes are suppressed or a protein is removed. There is research, for example, into the identification and removal of an allergenic protein from soybean using recombinant DNA technology[16] and similar work is ongoing for peanut.[17]

Although this review concerns the allergenic potential of GM foods, it should be highlighted that toxicity of a new gene product is another major

concern. This can occur because the transgene encodes a toxin; or transgenesis may cause an unintended effect such as silencing of suppressor genes; or there is overexpression of inherent toxins of the host. Although the level of risk for a single product is readily evaluated by standard toxicological tests, complex admixtures of chemicals as in GM foods are more difficult to analyse. Despite these difficulties, there is very little documented peer-reviewed literature to show that GM crops are potentially toxic.[18] One paper reported in 1999 that rats fed with GM potatoes expressing the gene for the lectin *Galanthus nivalis* agglutinin developed gut mucosal damage,[19] but the data were subsequently discredited by the Royal Society.[20,21]

Regulation and safety testing

Definitive testing of new products for safety is complex and it is difficult to predict with complete certainty the potential for any protein to be a food allergen. Robust regulatory measures that include the use of validated scientific protocols for assessments should minimise the risk. Of note, GM crops are tightly regulated by the European Food Safety Authority, US Food and Drug Administration, the US Environmental Protection Agency, and the Animal and Plant Health Inspection Service under the US Department of Agriculture. Consequently, GM plants undergo extensive and detailed safety testing prior to commercialisation, but there is no international consensus on laboratory testing methods on GM foods.

The Codex Alimentarius Commission has adopted guidelines in an attempt to standardise pre-market risk assessment.[22] A number of other guidelines have also been published to evaluate allergenic potential.[23-25] For instance, there are some common features that many allergens share so new GM proteins can be checked against these characteristics on extensive databases. It should be possible, at least theoretically, to determine if a new GM protein is likely to be an allergen by comparing its amino acid sequence and structure with that of known allergens. For this bioinformatic strategy to be useful, there probably has to be a minimum cut-off of 35% homology over an 80-amino-acid window.[26] Other approaches include examining whether the serum of allergic individuals reacts with GM foods; and the use of animal models to screen GM foods for allergenicity. The use of animal models is controversial and some scientists believe that although they provide mechanistic information, their use to predict food allergies has not been validated.[26] Testing strategies are constantly evolving and each test when used alone has drawbacks. Nevertheless when used in combination, the current analytical tools offer a powerful screen for allergenic potential.

Safety assessment schemes generally follow the principles of substantial equivalence; if a new food is found to be substantially equivalent to an existing food, the new food is considered to be as safe as its conventional counterpart.[24,27-31] Safety assessments for GM foods consider seven domains, namely composition; dietary intake; nutritional data; toxicology; allergenic properties; and characteristics of the donor and host organisms.[30-32] To establish substantial equivalence, extensive comparative studies in both the GM and conventional food have to be conducted. If differences are discovered, further detailed analyses have to be performed. Studies of this type establish to a high degree of certainty that the level of safety of the new GM food is likely to be equivalent to that of non-GM foods. Such testing is not generally required for conventional foods, so there is a marked divergence in the regulatory control of these two different food groups.

Other measures have been used to improve the safety of GM crops in addition to the testing described above. They include measures to separate planting of GM crops from conventional crops.[33] At the very least, planting of GM and unmodified crops is separated by a buffer zone with size proportional to the distance pollen can travel. This precaution, however, can only be relative because how far pollens are carried by bees or other pollinators cannot be estimated with any certainty. Other techniques for containment are expensive but have included growing the crops in greenhouses, or in areas where no weed or food crops are grown. Genetic containment has also been tried. This involved the use of technology to limit transfer of pollens or to interfere with fertility and seed formation.[33]

Post-launch monitoring of consumers for evidence of previously unidentified allergenicity may be critical. Finally, mandatory labelling of GM ingredients has been enforced by legislation in some countries for the sake of transparency. Such ingredient listing and information facilitate tracing and recall if required.

Situation in China and in Hong Kong

China has a fifth of the world's population but only about 7% of its arable land. Food security is a national priority. In February 2016, state-owned ChemChina announced its bid to buy the pesticide- and seed-producing giant Syngenta, one of the biggest acquisitions in China's history. Technology and especially GM crops are viewed by China to be central to a sustainable future. Nonetheless there are major public health concerns about food safety in China including the side-effects and toxicity of GM foods.

China issued its first licence to a GM crop in 1997, namely cotton, that is now widely used. Papaya that are GM was approved 6 years ago but

China has since restricted the import of most GM foods[34] and regulations demand their mandatory labelling.[35] The Ministry of Agriculture has issued a list of GM foods that can be sold in China if clearly labelled and these include: soy products (soybean seeds, soybeans, soybean powder, soybean oil, and soybean meal); corn products (seed corn, corn, corn oil, and corn powder); rape products (planting seed of rape, rapeseed, rapeseed oil, and rapeseed meal); cotton seed; and tomato products (tomato seed, fresh tomatoes, and tomato paste).[36] It is generally accepted that China's slow adoption of GM rice and GM corn has had more to do with negative public pressures than scientific concerns. The formal policy address affirmed that the country will speed up innovative application of agricultural biotechnology breeding to develop new biological varieties that have important value for fostering a large and strong modern seed industry.[37,38]

Hong Kong has no commercial production of GM crops or livestock. Food products on shop shelves that contain GM food ingredients have been approved for human use by the authorities in their country of origin.

The Hong Kong SAR Government conducted a public consultation followed by an external regulatory impact assessment. This was completed in 2003, after which the Government issued guidelines for voluntary labelling of GM foods so consumers could make an informed choice. It is highly doubtful that a voluntary scheme for food labelling will provide the kind of reassurance the public demands. The Government also decided that it would be appropriate to consider introducing pre-market safety assessments to ensure the safety of GM foods.[39]

Conclusion

Allergies to non-GM foods are common—for example, peanut, shrimp, fish, and soft fruits—as seen in the oral allergy syndrome, so foods produced by both conventional breeding and GM technology have the potential to be allergenic. There are no persuasive data that GM foods pose risks that are anywhere comparable with those encountered daily from consumption of naturally occurring food allergens that are not banned. The recent introduction of kiwifruit has resulted in the appearance of new allergies, but they have not been removed from the market place. Instead food labelling is used to help the consumer avoid exposure if required. There is a continuing need to develop improved validated tools to predict allergenic potential of new GM proteins. Only then can scientific evidence be separated from the realms of fevered speculation. Greater public engagement, post-launch monitoring, and mandatory labelling of GM foods will also go a long way to reassure the community about their safety.

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