Food Science and Human Wellness 5 (2016) 116–123

Food Science and Human Wellness

www.elsevier.com/locate/fshw

Genetically modified foods: A critical review of their promise and problems

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Received 11 March 2016; accepted 29 April 2016
Available online 3 June 2016

Abstract

The term "genetic modified organisms (GMO)" has become a controversial topic as its benefits for both food producers and consumers are companied by potential biomedical risks and environmental side effects. Increasing concerns from the public about GMO, particularly in the form of genetic modified (GM) foods, are aimed at the short- and long-lasting health problems that may result from this advanced biotechnology. Complex studies are being carried out around the world independently to evaluate the advantages and disadvantages of GM foods. In this paper, we attempt to summarize up-to-date knowledge about the benefits and potential problems of GM food. We also introduce some recent technological developments in GM foods and their impact in the field.

Keywords: Genetic modified (GM) food; Transgenic; Safety; DNA; CRISPR-Cas9

1. Introduction

In July 2011, a group of protesters from Greenpeace, a non-governmental, environmental organization, broke into an experimental farm of the Commonwealth Scientific and Industrial Research Organization (CSIRO), an Australian federal government agency for scientific research, and destroyed the entire crop of genetically modified wheat. In August 2013, a research field of Golden Rice managed by the Philippine Government's International Rice Research Institute (IRRI), and other public sector partners was attacked by anti-GMO (Genetically-Modified Organisms) activists. "Golden Rice" expresses high levels of beta-carotene (a precursor of vitamin A) thanks to its modified genetic properties. After 25 years' bench work in the laboratory, Golden Rice, designed as a cheap and effective way to deliver dietary source of vitamin A for developing areas of the world, had finally reached the point where field trials were practical [1]. Although different in many ways from the 2011 CSIRO break-in, the 2013 incident triggered strong condemnation by the scientific community, though that reaction failed to achieve consensus among public voices. The fundamental reason for the failure is the continuing lack of comprehensive understanding of current agricultural problems and the nature of GMO. In this review, starting with the history of GMO, we address the motivation for GMO (including GM foods), their benefits and risks, as well as the impact of recent technology developments on GMO/GM foods.

2. What are GMOs and GM foods?

Genetic modification is a biological technique that effects alterations in the genetic machinery of all kinds of living organisms. GMO is defined as follows by WHO (World Health Organization): "Organisms (i.e. plants, animals or microorganisms) in which the genetic material (DNA) has been altered in a way that does not occur naturally by mating and/or natural recombination" [2]. The definition seeks to distinguish the direct manipulation of genetic material from the millennial-old

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Peer review under responsibility of Beijing Academy of Food Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.fshw.2016.04.002

Table 1
Crucial steps in the history of genetic modification.

Time	Event	Time	Event
1859	Charles Darwin published the first edition of "On the Origin of Species"	1980	Jon W. Gordon et al. made first transgenic mice
1865	Gregor Mendel discovered that heredity transmitted in units	1983	Kary Mullis invented PCR (polymerase chain reaction)
1869	Frederick Miescher isolated DNA	1985	Generate the first transgenic domestic animal, a pig
1902	Walter Sutton developed chromosome theory of inheritance	1987	First human genetic map was discovered
1911	Thomas Hunt Morgan showed chromosomes carry genes	1990	Human genome project was launched
1941	George Beadle and Edward Tatum Hypothesized one gene one enzyme theory	1991	First gene therapy trials on humans
1944	Oswald Avery et al. demonstrated DNA can transform the properties of cells	1992	The second-generation genetic map of human genome was developed
1952	Alfred Hershey and Martha Chase showed that genes are made of DNA	1993	FDA approved the use of Bovine somatotropin (bST) to increase milk production in dairy cows
1953	Francis H. Crick and James D. Watson described the double helix structure of DNA	1994	FDA approved the sale of the first GM food, the FLAVR SAVR tomato
1958	Matthew Meselson and Franklin Stahl discovered the semiconservative replication of DNA	1996	The birth of Dolly the sheep, the first cloned animal
1961	Sydney Brenner et al. reported that mRNA ferries information from DNA	1997	The *E. coli* genome was sequenced
1966	Marshall Nirenberg et al. cracked genetic codes	1998	*M. tuberculosis* Bacterium and Roundworm *C. elegans* were sequenced
1968	Steward Linn and Werner Arber described first restriction enzyme	1999	The first human chromosome, chromosome 22 was decoded
1973	Stanley Cohen and Herbert Boyer invented DNA cloning	2002	Mouse genome working draft was assembled
1977	Richard Roberts and Phil Sharp discovered introns	2003	The human genome sequencing was completed

This table is modified based on http://www.gmeducation.org/faqs/p149248-20brief%20history%20of%20genetic%20modification.html and https://www.genome.gov/Pages/Education/GeneticTimeline.pdf.

practice of improvement in the genetic stock of plants and animals by selective breeding. With DNA recombinant technology, genes from one organism can be transferred into another, usually unrelated, organism.

Similarly, the FAO (Food and Agriculture Organization of the United Nations) and the European Commission define a GMO as a product "not occur naturally by mating and/or natural recombination" [3]. "GM foods" refer to foods produced from genetically modified plants or animals.

However, Oliver [1] pointed out the aforementioned definitions are somewhat imperfect, giving Triticale as an example. Triticale is a grain widely used in bread and pasta. It was developed the 19th century by crossing wheat with rye (a conventional, selective breeding approach). However, the resulting hybrid is sterile, and in the 1930s, the chemical colchicine was used to generate polyploid embryo cells, which are fertile. Triticale would seem unambiguously to fit the definition of a GMO, even if the genetic modification is somewhat primitive by current molecularly biological standards. Thus, Oliver suggests "biotechnologically modified organism" as a closer definition for GMO [1].

3. History of GM foods

The genesis of DNA modification technology can be traced back to 1944, when scientists discovered that genetic material can be transferred between different species [4]. Several hallmark papers paved the way to the modern science of molecular biology. In 1954, Watson and Crick discovered the double helix structure of DNA, and the "central dogma" – DNA transcribed to messenger RNA, translated to protein – was established. Nobel Laureate Marshall Nirenberg [5] and others had deciphered the genetic code by 1963. In 1973, Cohen et al. [6] developed DNA recombination technology, showing that genetically engineered DNA molecules can be transferred among different species.

The history really begins with Charles Darwin's notions of species variation and selection. Table 1 presents a sort of time-capsule of the seminal discoveries that are crucial to modern genomics.

The first genetically modified plants – antibiotic resistant tobacco and petunias – were produced by three independent research groups in 1983 [7–9]. Scientists in China first commercialized genetically modified tobacco in early 1990s. In 1994 the US market saw the first genetically modified species of tomato with the property of delayed ripening approved by the Food and Drug Administration (FDA). Since then, several transgenic crops have received FDA approvals, including "Canola" with modified oil composition, cotton and soybeans resistant to herbicides, etc. GM foods that are available in the market include potatoes, eggplants, strawberries, carrots, and many more are in pipeline [10].

4. Do we need GM foods?

Before starting discussing the merits and demerits of GM foods, it is important to set forth why there is such great effort to develop them. There are three major challenges we are facing that motivate our resort to the new technology for help.

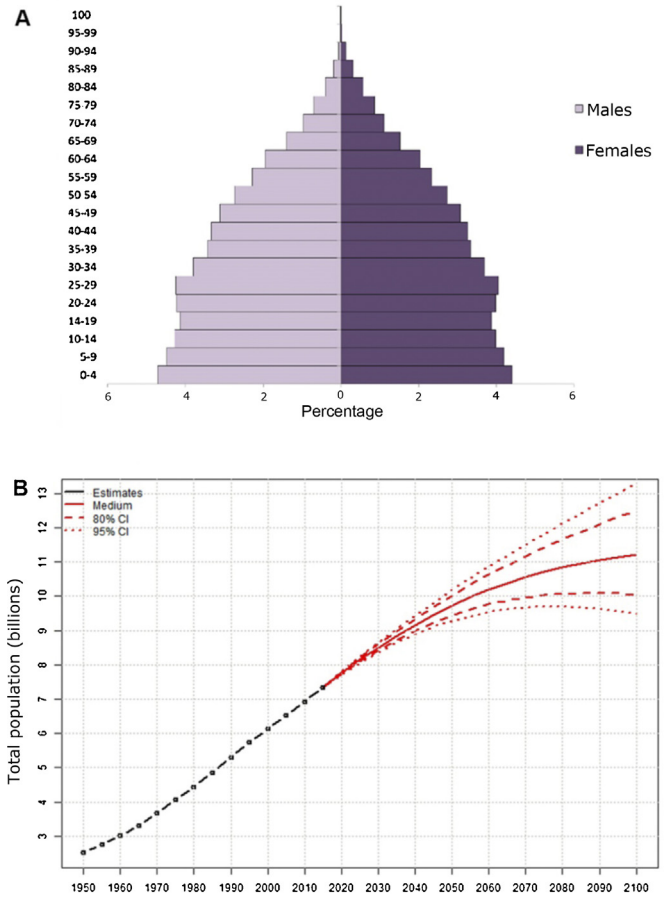

Fig. 1. Distribution and projected growth of world's population. (A) Distribution of the world's population by age and sex, 2015 Source: United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision. New York: United Nations. (B) Population of the world: estimates, 1950–2015, medium-variant projection and 80% and 95% confidence intervals, 2015–2100.
(Charts are adopted from http://esa.un.org/unpd/wpp/publications/files/key_findings_wpp_2015.pdf).

4.1. Expansion of population

The current global human population is approximately 7.35 billion (United Nations Department of Economic and Social Affairs/Population Division World Population Prospects: The 2015 Revision, Key Findings and Advance Tables). Fig. 1A shows the distribution of population around the world (upper panel). Although growth rate of the world population has slowed in recent years (1.24% per year 10 years ago versus 1.18% per year in recent years), an annual addition of 83 million people is expected. The estimated global population will be 8.5 billion in 2030, and 9.7 billion in 2050 (Fig. 1B). The expansion of population is one of the major contributors to undernourishment around the world. In 2016, the U.N. Food and Agricultural Organization (FAO) reported that 795 million people in the world were undernourished, among which 780 million people in developing regions [11]. Therefore the eradication of hunger should be a priority of policy-making.

Arguably the most realistic solution for matching increased global demand for crops is to boost the crop yields on currently cultivated land. Currently, the rate of increase in crop-yield is less than 1.7% whereas the annual increase in yield needs to be 2.4% to meet the demands of population growth, improved nutritional standards and decreasing arability (see below) [12]. This is a daunting task, which seems only achievable by means of optimization of crop genetics coupled with quantitative improvements in management of the agricultural system.

4.2. Decrease in arable land

FAO predicted that the finite amount of arable land available for food production per person will decrease from the current 0.242 ha to 0.18 ha by 2050 [13]. This problem confounds those of population growth and malnutrition. Yet our ability to bring additional acreage under cultivation seems limited. The alternative is greater yield per acre, which in turn must come from greater agriculture inputs, such as fertilizer, water, pest and weed control – and/or genetic improvement [1]. This scenario is compounded by several complicating factors: (1) the increased demand for biofuel and feedstock production; (2) accelerated urbanization; (3) land desertification, salinization, and degradation; (4) altered land use from staple foods to pasture, driven by socioeconomic considerations; (5) climate change; (6) water resource limitation.

4.3. Bottleneck of conventional and modern breeding

Conventional breeding relies on sexual crossing of one parental line with another parental line, in hopes of expressing some desired property (e.g. disease resistance) [1]. To select for the desired trait and to dilute irrelevant or undesired traits, breeders choose the best progeny and back-cross it to one of its parents (plant or animal). The process usually takes several years (depending on generational time, e.g. 10–15 years for wheat) before actual expression of the desired trait that can be assessed, and further expanded by conventional breeding to commercially useful numbers. Besides the inherently long generation times, the following facts limit the development of conventional breeding: Prerequisite to breeding strategies is the existence of genetic variation that is, existence of an available gene-pool manifesting the desired traits, and sexual compatibility of organisms with those traits. In fact, nowadays genetic variety has dwindled (probably as a result of past efforts at optimization), thus we operate in a restricted space for improvement. Modern methodologies can increase this space by utilizing chemicals or radiation to introduce new mutational variation. However, these are blunt instruments that result in improved traits only by random chance and sparse luck. Indeed, the non-selectivity of these methods probably extend the breeding timeline [1].

Taking these facts into account, the emergence of biological technologies and the development of GM foods promise to reduce dramatically production timelines to new strains, and to provide us with optional strategies to achieve sustainable global food security.

5. Generation of GM crops

In order to generate GM foods, researchers need to introduce the gene(s) coding for certain traits into a plant cell, and then regenerate a plant through tissue culture. When and where the transferred gene is expressed is usually inherent in the scheme to optimize the property of the product. Generally speaking, there are three ways to modify genes in the cells.

5.1. Directly transfer DNA

The most widely used technique for delivering exogenous DNA is microparticle bombardment. The technique was developed in the late 1980s by Sanford [14]. Naked, engineered DNA is coated on gold or tungsten microparticles, which, in turn, are delivered at high velocity into targeted tissues, such as embryonic tissues from the seed or meristems, propelled by pressurized helium. There are other ways to deliver DNA into plant cells, including electroporation (letting the negatively charged DNA move down an electric potential gradient) into protoplasts, microinjection, chloroplast transformation, silicon-carbide slivers, mesoporous silica nanoparticles, etc. [15]. However, particle bombardment remains more effective at transferring large DNA fragments – even whole chromosomes – simultaneously [16].

5.2. Indirectly using bacterial vehicle

The use of *Agrobacterium tumefaciens* opened a new era for inserting exogenous genes into plant cells. The soil bacterium *A. tumefaciens* infects plants, forming a gall at the crown. The bacteria actually alter the genome of the plant, not only causing proliferation of the plant cells, but also enabling the plant to produce modified amino acids as a specialized food source for themselves. The bacteria possess a tumor-inducing plasmid ("Ti-plasmid"), which enable them to accomplish gene-insertion; researchers hijack the plasmid by inserting "designer gene's" into the T-DNA (transfer DNA) section of the Ti-plasmid.

5.3. Direct editing of genomic DNA

In 2012, the "CRISPR-Cas9" system was developed. It constitutes a revolutionary genome editing tool, and provides another method to alter genes in various type of cells [17,18]. This technique dramatically increases the efficiency of genetic engineering, making the work with plants much easier [19].

Cas9 is a DNA endonuclease originally found in bacteria, where it protects the host bacteria from invading DNA molecules (e.g. viruses). The endonuclease is guided to the invading/targeting DNA by a special "guide RNA" (gRNA), whose sequence is complementary to the invading sequence to be expunged. Thus guided by the offensive, Cas9 utilizes its two active sites to cleave both strands of the double-stranded DNA. The newly formed DNA double-stranded breaks (DSBs) are then repaired by two different mechanisms inside cells: The "non-homologous end joining" (NHEJ) mechanism can cause a small deletion or random DNA insertion, leading to a truncated gene or knockout, while the "homologous recombination" (HR) mechanism allows the addition of a donor DNA into the endogenous gene at the break site (Fig. 2).

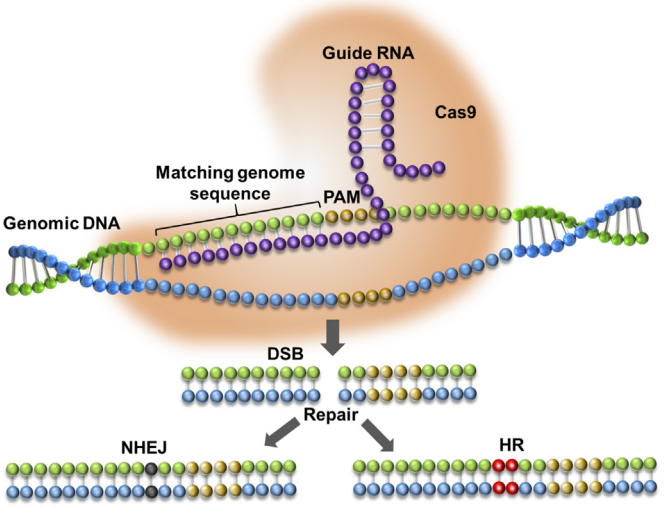

Fig. 2. Mechanism of CRISPR-Cas9 gene-editing technique. Black dot: InDel resulting in premature stop codon. Red dots: Precise gene editing and addition of a donor gene. DSB: double-stranded breaks (DSBs); NHEJ: the non-homologous end joining; HR: the homologous recombination.
Figure is adapted from Transomic (http://www.transomic.com/).

The rapid development of these cutting-edge biotechnologies has also challenged the food regulation law. The US Department of Agriculture (USDA) has determined that the current regulations are not suitable for several genome-edited crops, therefore, on November 18th, 2015, the USDA released provisional plans to revise its guidelines for GM crops. GM foods produced in the U.S. are listed in Table 2.

6. Benefits of GM foods

6.1. Agronomic benefits

1996–2012 saw an increase of more than 370 million tons of food crops. One-seventh of the increased yield is attributed to GM crops in the U.S. To achieve an equal increase in yield as delivered by GM crops, it is estimated that an addition of more than 300 million acres of conventional crops would have been needed [20,21]. These additional 300 million acres would necessarily be lands requiring more fertilizer or irrigation, or carved out tropical forests. Such conversion of land would generate serious ecological and environmental stress to the world. A report from Graham Brookes and Peter Barfoot (*17*) arrived as similar conclusions: for the period 1996–2013 they estimate that biotechnology was responsible for additional global production of 138 million tons of soybeans, 274 million tons of corn, 21.7 million tons of cotton lint, and 8 million tons of canola. If those biotechnologies had not been available, to maintain equivalent production levels would have required an increment of 11% of the arable land in the US, or 32% of the cereal area in the EU.

Table 2
Summary list of approved GM crops. List based on the GM approval database (http://www.isaaa.org/gmapprovaldatabase/cropslist/default.asp).

Scientific names	GM traits	Trade name
Apple (*Malus* × *Domestica*)	Antibiotic resistance, non-browning phenotype	Arctic™"golden Delicious" Apple, Arctic™"Granny Smith" Apple.
Argentine Canola (*Brassica napus*)	Modified oil/fatty acid, antibiotic resistance, glufosinate herbicide tolerance, fertility restoration, male sterility, oxynil herbicide tolerance, glyphosate herbicide tolerance	Laurical™Canola, Optimum Glycanola, Roundup Ready™Canola, Liberty Link™Independence™, InVigor™Canola, Liberty Link™Innovator™, TruFlex™Roundup Ready™Canola, Phytaseed™Canola, Navigator™Canola
Bean (*Phaseolus vulgaris*)	Viral disease resistance	N/A
Eggplant (*Solanum melongena*)	Lepidopteran insect resistance, antibiotic resistance	BARI Bt Begun-1, -2, -3 and -4
Maize (*Zea mays* L.)	Male sterility, fertility restoration, visual marker, modified alpha amylase, mannose metabolism, glufosinate herbicide tolerance, Lepidopteran insect resistance, glyphosate herbicide tolerance, coleopteran insect resistance, multiple insect resistance, sulfonylurea herbicide tolerance, antibiotic resistance, 2, 4-D herbicide tolerance, drought stress tolerance	32138 SPT maintainer, Enogen™, Agrisure®Duracade™, Agrisure®Duracade™5122, Agrisure®Duracade™5222, Herculex™RW, Herculex™RW Roundup Ready™2, Optimum™GAT™, Agrisure™GT/CB/LL, Agrisure™3000GT, NaturGard KnockOut™, Maximizer™, Starlink™Maize, Enlist™Maize, Bt Xtra™Maize, Roundup Ready™Maize, Agrisure™GT, Roundup Ready™YieldGard™maize, Agrisure™RW, YieldGard™, MaizeGard™, YieldGard™VT Triple, YieldGard™Rootworm RW, MaxGard™, YieldGard™Plus, YieldGard™Plus with RR, YieldGard™RW+RR, Genuity®DroughtGard™, YieldGard™ VT™Rootworm™RR2, Genuity®VT Triple Pro™, Genuity®VT Double Pro™, Genuity®SmartStax™, Power Core™, InVigor™Maize, YieldGard™CB+RR, Liberty Link™Maize, Herculex™I/CB, Optimum™Intrasect Xtreme/XTRA, Herculex XTRA™/RR/I RR, Optimum™TRIsect, Hysyn 101 RR Roundup-Ready™, Intacta™Roundup Ready™ 2 Pro
Melon (*Cucumis melo*)	Delayed ripening/senescence, antibiotic resistance	N/A
Papaya (*Carica papya*)	Viral disease resistance, antibiotic resistance visual marker	Rainbow, SunUp, Huanong No. 1
Plum (*Prunus domestica*)	Viral disease resistance, antibiotic resistance visual marker	N/A
Polish canola (*Brassica rapa*)	Glufosinate herbicide tolerance, glyphosate herbicide tolerance	Hysyn 101 RR Roundup-Ready™
Potato (*Solanum tuberosum* L.)	Coleopteran insect resistance, antibiotic resistance, modified starch/carbohydrate, reduced acrylamide potential, black spot bruise tolerance, viral disease resistance	Lugovskoi plus, Elizaveta plus, Starch Potato, Atlantic NewLeaf™potato, New Leaf™Russet Burbank potato, Innate™Russet Burbank Potato, Innate™ G/H Potato, Hi-Lite NewLeaf™Y potato, Innate™Atlantic Potato, New Leaf™ Y Russet Burbank potato, New Leaf™Plus Russet Burbank potato, Shepody NewLeaf™ Y potato, Innate™Snowden Potato
Rice (*Oryza sativa L.*)	Anti-allergy, antibiotic resistance, Lepidopteran insect resistance, Lepidopteran insect resistance, glufosinate herbicide tolerance	BT Shanyou 63, Huahui-1, Liberty Link™rice
Soybean (*Glycine max* L.)	Modified oil/fatty acid, antibiotic resistance, visual marker, glufosinate herbicide tolerance, sulfonylurea herbicide tolerance, glyphosate herbicide tolerance, 2, 4-D herbicide tolerance, isoxaflutole herbicide tolerance, drought stress tolerance, Lepidopteran insect resistance, dicamba herbicide tolerance, mesotrione herbicide tolerance	Liberty Link™soybean, Cultivance, Enlist™Soybean, Treus™, Plenish™, Optimum GAT™, Roundup Ready™ soybean, Verdeca HB4 Soybean, Intacta™Roundup Ready™ 2 Pro, Vistive Gold™, Genuity®Roundup Ready™ 2 Xtend™, Genuity®Roundup Ready™ 2 Yield™, Herbicide-tolerant Soybean Line
Squash (*Cucubita pepo*)	Viral disease resistance, antibiotic resistance,	N/A
Sugar Beet (*Beta vulgaries*)	Glyphosate herbicide tolerance, Visual marker, Antibiotic resistance	InVigor™sugarbeet, Roundup Ready™sugarbeet, Liberty Link™sugarbeet
Sugarcane (*Saccharum* sp.)	Drought stress tolerance, antibiotic resistance	N/A
Sweet pepper (*Capsicum annuum*)	Viral disease resistance	N/A
Tomato (*Lyopersicon esulentum*)	Delayed ripening/senescence, antibiotic resistance, Lepidopteran insect resistance, delayed fruit softening, viral disease resistance	FLAVR SAVR™
Wheat (*Triticum aestivum*)	Glyphosate herbicide tolerance	Roundup Ready™wheat

6.2. Economic benefits

From 2006 to 2012, the global increase in farm income from GM food had reached $116 billion, almost triple that of previous 10 years [20,21]. According to the estimation from James and Brookes, about 42% of the economic gain was from the increased yield due to advanced genetics and resistance to pests and weeds. The decreased costs of production (e.g. from reduced pesticide and herbicide usage) contributed the remaining 58%.

6.3. Modification of the chemical composition in food

Some genetic modification is specifically targeted to enrich certain nutrients or substances having high therapeutic and pro-health value, including vitamins A, C, E, unsaturated fatty acids, alimentary cellulose and probiotics [22]. The aforementioned "Golden Rice" is a significant example. It ameliorates malnutrition in an effective and economic way. Similarly, using this biotechnology, researchers can also alter the amino acid composition of proteins as well as the content of carbohydrates. The former is exemplified by sweet lupine, of which the content of methionine is enriched [23,24]. The generation of Amflora, a modified potato variety, is a good example for the latter scenario.

Enhanced nutritional value in transgenic products has been obtained by manipulating their composition of carbohydrates. Let us consider further the example of Amflora. The bulk of polysaccharides in the potato-bulb is formed by two types of starch: amylose and amylopectin. Amylose is useful only as food starch, while amylopectin is widely used in the production of non-food starch, paper, and in textile processing. The synthesis of starch requires various enzymes, which include a granule-bound starch synthase (GSBB), the primary function of which involves the production of amylose. In the absence of GSBB, amylopectin is produced exclusively. Exploiting this knowledge has led to methods to modify the composition of potato starch. The transgenic process involves the introduction into potato bulbs of an additional copy of the GSBB-coding gene. Counter intuitively, the extra gene in fact suppressed expression of GSBB, by a process know as "co-suppression", a.k.a. "gene silencing". The resultant Amflora potato is with decreased amylose, but rich in amylopectin [25].

6.4. Improvement in food processing

The GM technology can also be employed to facilitate food processing. A notable achievement is "Flavr Savr" tomatoes. They were produced by the California company, Calgene, in 1992. The genetic alteration consists of introduction of an antisense gene, which suppresses the enzyme polygalacturonase; the consequence is to slow down the ripening of tomatoes and thus allow longer shelf life for the fruits. The composition in potato bulbs has also been altered by gene editing. For instance, using a cyclodextrin glycosyltransferases gene from bacteria, potatoes exhibit greater stability of brightness factors and, thus, a more attractive appearance [26].

Genetic modification is not limited to plants, but is also applied to animal products. Some researchers are exploring transgenic fish with a view to enhancing the generation of growth hormones to accelerate growth and body mass [27–29]. Very recently the FDA (the US Food and Drug Administration) has approved the first genetically engineered animal, "AquAdvantagea" salmon – a fast-growing salmon – for human consumption in the United States. The decision was made after two decades of regulatory limbo. Because the fish grow to full size in 18 months, rather than 3 years, and with less demand for food resources per kilogram of harvested fish, farming "AquaAdvantagea" may ease pressure caused by heavy fishing of wild populations. Meanwhile, quite a few attempts have been made to generate milk with decreased content of lactose or humanized bovine milk [29,30].

6.5. Products for therapeutic purposes

Genetic engineering techniques enable the expression of viral or bacterial antigens in the edible portion of plant cells [28,31,32]. In theory, thus, transgenic foods could serve as oral vaccines, capable of stimulating the immune system, via mucosal immunity, to produce antibodies. A variety of crops (e.g. rice, maize, soybean and potatoes) are under study as potential bearers of edible vaccines against different infections, including *Escherichia coli* toxins, rabies virus, *Helicobacter pylori* bacteria, and type B viral hepatitis [27,28,31–34].

7. Potential risks of GM foods

The debates over GM foods focus mostly on uncertainties concerning the potential adverse effects of GM foods on human health and environmental safety. The anxiety among consumers can be attributed to four sources: the difficulty of the scientific community in explaining concisely to the lay public the biological techniques involved; concerns about the improper dissemination of GM foods; and the ethical principles inherent in traditional food processing; the misgivings with regards to the adequacy of evaluation of the GM foods [22,35,36].

7.1. Health risks associated with GM foods

Three major health risks potentially associated with GM foods are: toxicity, allergenicity and genetic hazards. These arise from three potential sources, the inserted gene and their expressed proteins per se, secondary or pleiotropic effects of the products of gene expression, and the possible disruption of natural genes in the manipulated organism [10].

"Starlink" maize provides an example of a food hazard caused directly by the expression of the inserted gene [29,35,37–39]. The modified plant was engineered with genetic information from *Bacillus thuringinesis* in order to endow the plant with resistance to certain insects. The inserted gene encodes a protein, called Cry9c, with pesticidal properties, but with an unintended, strong allergenicity. Several cases have been reported of allergic reaction in consumers after consuming the "Starlink" maize.

Modification on the expression level of natural components of the manipulated organism can also exacerbate allergy. One example is the production of soybeans enriched in the amino

acid methionine. The enhanced synthesis of this amino acid is the result of a gene isolated from Brazil nuts. As a consequence, some consumers allergenically sensitized to these nuts have allergic reactions to the transgenic soybean.

Secondary and pleiotropic effects are much less straightforward to recognize than direct effects of the gene or its products. The modified gene may encode an enzyme involved in otherwise natural metabolic pathways of the modified organisms. Such changes might alter the levels of other metabolites, including toxic ones, at some "metabolic distance" from actual metabolic perturbation. Connecting the causative dots presupposes an intimate understanding of the biochemical and regulatory pathways – which may be beyond current comprehension.

Another scenario of potential risk is that the inserted gene might disrupt the integrity of existing genomic information in the plant, leading to inactivation, or other modulation, of endogenous genes. Again, such a disruption might be envisioned to activate (or deactivate) metabolic processes involving product or toxins, or their detoxification – in any case by events far removed from the known and intended effect of the inserted gene, and thus confounding our ability to draw a causal connection between the inserted gene and the alleged effect.

7.2. Ecological risks associated with GM food

7.2.1. Selection of resistance

Currently, the majority of GM foods are aimed at endowing the altered plant two desirable properties – pest-resistance or herbicide-resistance. Insect-resistant crops are typically designed to express insecticidal crystal proteins (CRY), naturally produced by the soil bacterium *Bacillus thuringiensis* (Bt). Herbicide-tolerant crops are designed to express enzymes that protect against herbicides (primarily the glyphosate Roundup^{TM}), often by their ability to degrade the herbicide. The strategy is clever: the human-applied herbicide kills the weeds, but does not harm the crop-plant.

The use of these two technologies greatly reduces immediate input costs incurred by farmers – the battle against weeds becomes much less labor-intensive, and the battle again insects requires much less expensive and toxic pesticides. But, in the long-term, can these strategies really out-fox Nature, in her ineluctable progress toward selecting better-adapted species? When heartier weeds and insects evolve, what then? It seems almost inevitable that, in a few years, insects and weeds will respond to the human-made pressures in their habitats by evolving ways to nullify our clever design of transgenic crops [10].

7.2.2. Disruption of the food web

Another issue is the possibility that the insect-resistant plants might increase the number of minor pests while reducing the major type of pest. The scenario here is that the pest population might shift from those put-off by the engineered plants to other, undaunted species. This shift, in turn, might unleash a pervasive disruption of the entire food chain, with new predators of the new insect species, and so on up to the top of the chain [10]. Or the disruption might work in the other direction, whereby residues of herbicide or insect resistant plants might generate negative effects on organisms (e.g. bacteria, fungi, etc.) found in surrounding soil [40].

7.2.3. Resistance to antibiotics

Development of resistance to antibiotics is a scourge well known to medical science, and is traceable to the over-use of therapeutic antibiotics in medicine and agriculture. In the processes of genetic modification, antibiotics are also frequently employed, typically as selection markers, to distinguish successfully transformed bacteria from those in which the transfecting genes did not take hold. Thus, the machinations to genetically modify an organism carries the risk of transferring the genes of antibiotics resistance into the benign bacteria comprising the microflora of human and animal gastrointestinal tracts, or, worse yet, to pathogenic bacteria harbored by the consumer of GM a food, because bacteria, good and bad, are quite capable of shuttling useful genes – like those that protect them from nasty antibiotics – around by horizontal transfer between species [29,41–43].

8. Conclusions

The question of whether or not humans should eat food from genetically modified organisms – and, therefore, if they should develop and propagate them – is clearly not amenable to a simple "yes" or "no". Indeed, a wise answer comprehends a diverse array of scientific expertise, not only in files of molecular biology, but also in agricultural economics, animal and microbial ecology, food technology, and immunology – a breadth of expertise unlikely to be found in one person.

The arguments, pro and con, reverberate the whole history of human technological development, pitting the clear advantages of intended consequence against the mucky possibilities of unintended consequence. One needs to think only of the fossil-fueled industrial revolution versus global warming. Or of that much-heralding replacement for fossil fuel, nuclear power generation, versus Tokushima. Certainly, many of the risks of GM crops, noted above, are speculative, but they are scientifically plausible, and offered in good faith. Ignoring them in a euphoria of immediate advantage is equally unscientific.

Drawing from past experience it seems unlikely the technological momentum toward genetically modified foods can be stopped dead in its tracks. Or should be. The immediate advantages are too tangible to ignore or set aside out of fear of the unknown and unintended disadvantages.

With un-Hamlet-like indecisiveness, we suggest evaluating, gingerly, and always with keen (and collective) circumspection toward the first signs of problems.

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