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Humans began cultivating plants roughly 10,000 years ago when the estimated global population was less than 10 million (24). Early farmers had to learn which plants could be cultivated and how plants could be improved through breeding by trial and error (7). Evidence suggests that progenitors of modern varieties of wheat and barley were first domesticated nearly 10,000 years ago in the Middle East. Soybeans were domesticated approximately 5,000 years ago and rice approximately 6,000 years ago in Asia. Early varieties of maize were grown in Central America nearly 9,000 years ago (12). Although varieties of these common crops are genetically diverse, major changes in the genetics of domesticated crops have been sporadic (e.g., soybean) (14). Modern common bread wheat is a hexaploid (6n) species that has three times as many chromosomes and genes as its probable wild progenitor, while pasta wheat (durum) is tetraploid (4n). Hexaploid wheat varieties were derived from naturally hybridized grass family relatives represented by diploid (2n) and tetraploid (4n) species (8).

Most of the genetic diversity that has improved agricultural production throughout the history of farming was developed through natural mutations and selective breeding. However, since the early 1900s plant scientists have used chemical and radiation mutagenesis to increase genetic diversity (18). We know that the majority of mutations are harmful, and plant breeders work hard to select only those that are beneficial. This process has helped feed a growing human population, which is estimated to have been 300 million 2,000 years ago and is now more than 7 billion. However, methods used in the past to improve agricultural production are unlikely to keep pace with the current growth rate of the human population.

Growing Challenges for Food Production

Norman Borlaug won the Nobel Peace prize in 1970 for his efforts that led to the "green revolution:' In a speech reviewing 60 years of agricultural improvements (Table I), he credited improved plant genetics, increased use of irrigation, increased and efficient use of fertilizers, and increased mechanization as the major factors leading to the tripling of production of wheat and rice in Asia between 1960 and 2000 (1). Historically, genetic changes have been achieved by introducing unknown changes in genes through crossbreeding with wild relatives, development of hybrid varieties, and mutations induced by chemicals or radiation followed by careful breeding for selection. Borlaug noted that more precise genetic modification (GM) technology will be needed to maintain a sufficient food supply to feed the growing human population, which is expected to reach 10 billion by 2050.

Today, agricultural and food supply systems around the world are being challenged by political and economic barriers that are slowing or blocking the introduction of commonly consumed varieties of plants and animals that have been improved by highly specific GM. This is occurring at a time when the world population continues to grow, per capita consumption of resources is growing even faster, and prime agricultural land is being converted to urban or industrial uses. In addition, growing concerns about the environmental risks associated with the use of chemical pesticides, herbicides, and fertilizers are pushing farmers to reduce inputs that have helped raise productivity over the past 100 years. Fewer people are willing or able to work as farmers, and meeting growing demands requires continued improvements in the efficiency of food production. Rising food costs associated with crop production on marginal

farmland, crop failures due to changing weather patterns, high transportation costs, and energy use could be partly mitigated by the improvements in agricultural efficiencies offered by some GM crops. While there is a growing demand for and supply of organic foods, it is not clear that organic methods can meet current and future demands and supplant industrial agriculture, which has become the dominant production method. In addition, some GM varieties have been demonstrated to reduce the need for applied chemical pesticides and, thus, are environmentally beneficial.

As the human population continues to grow, we are not only increasingly converting farmland to urban uses, more people are eating meat, which is not energetically efficient. To compensate, we need to increase the rate of crop improvements, and as argued by Norman Borlaug, we need to use all available genetic tools, in cluding bio-

technology (genetic engineering), and improve use of chemical fertilizers, water, and mechanization to meet growing demands.

Importance of Genetic Complexity and Diversity of Non-GM Plants

Genetic diversity is essential to allow efficient growth of crops under diverse environmental conditions (e.g., day length, temperature, moisture level, soil type, pests, and disease conditions). Significant increases in yield have been achieved by combining different genetic types in parent lines and even more through hybrid generation from 1930, when the average corn production in the United States was 30 bu/acre, to 2004, when the average was 150 bu/acre (25). Hybrids of corn are produced by crossing genetically diverse parents to produce high-yielding seeds that generally outperform inbred line yields. Although hybrid seeds cost more, the increased yield usually pays farmers a dividend. Recent work also has demonstrated that inbred parental lines have substantial genetic diversity (33).

While great improvements have been made possible by advanced molecular breeding and selection, the introduction of genes from other species has opened up the possibility of developing plants that could never be achieved through breeding alone (e.g., resistance to the European corn borer and corn rootworm by the introduction of genes from the bacterium *Bacillus thuringiensis*). The safety of bacterial pesticides has been studied, and they are regulated by the U.S. Environmental Protection Agency (EPA)—the same agency that now regulates insect-resistant GM crops (23). The methods of using plant breeding, genetic engineering, and organic farming should be complementary, and the safety assessment of biopesticides should be similar because the active ingredients are the same.

Introducing New Traits Through Biotechnology

Watson and Crick won the Nobel Prize in 1963 for describing the basic structure of DNA polymers in 1953 (37). DNA is made up of unique extended sequence arrangements of four simple nucleotides (ATGC). They suggested a model structure of amino acids defined by a triple nucleotide codon arrangement, which with the anti-parallel DNA strands allowed accurate replication of the chromosomes. Of course, more details were later identified by other scientists (36). Understanding the structure of DNA was essential to enable biotechnology, and work by other scientists was necessary to develop many of the molecular tools used in the 1960s and early 1970s that led to the production of the first specifically genetically modified plants in the 1970s.

Contribution of GM Plants to the Food and Fiber Supply

Scientists around the world have been developing potentially useful GM crops since the early 1990s. Many of these GMOs will never be used commercially because they will fail to function, will not meet regulatory health or environmental safety criteria, or the value of the crop would not meet the costs of development and regulatory studies. However, some could be successful. The area of land cultivated in GM crops in 2012 surpassed 160 million hectares (17). Almost all of the approved GM plants have been invented or the rights purchased by large corporations with sufficient infrastructure and capital to complete registrations. Information about specific plants, crops, and approvals is available from the Center for Environmental Risk Assessment (CERA) (3) and the International Service for the Acquisition of Agri-biotech Applications (16). CERA lists 109 GMOs approved for food or feed in the United States, including alfalfa, canola, chicory, cotton, flax, linseed, maize, papaya, plum, potato, sugar beet, tomato, and wheat. A number of these GMOs are not currently commercially available (e.g., GM wheat).

In the United States, 88% of corn, 94% of cotton, and 93% of soybeans grown are GM varieties (35). The dominant GM traits are herbicide tolerance and insect resistance. Genes for the primary insect resistance traits have come from a bacterium (*B. thuringiensis*) that farmers have used as an organic pesticide since the 1940s (31). Insect-resistant plants reduce the need for chemical insecticides. A few viral resistance traits have been introduced that have reduced crop losses due to plant pathogens such as *Papaya ringspot virus, Potato leafroll virus,* and *Potato yellows virus* (3). However, a number of GMOs that were approved in the United States between 1995 and 2013 have not been approved for growing or importation in many parts of the European Union and some other countries, even though they were tested prior to commercial release and found to be as safe as conventionally produced varieties using evaluations recommended by the Codex Alimentarius Commission guidelines (4).

New GM developments include nutritionally enhanced commodity crops that can provide essential vitamins or precursors (e.g., rice and maize with high 13-carotene contents), as well as minerals (e.g., rice with high iron content), at lower costs compared with alternative food supplements. The Gates Foundation (www.gatesfoundation.org), the US. Agency for International Development (USAID), HarvestPlus, and other organizations are working to increase food security and nutrient availability using a variety of techniques to improve food crops, including genetic modification.

General Food Safety

The US. Food and Drug Administration (FDA) recognizes that all foods have inherent risks for some individuals. For example, individuals with diabe-

Table 1. Factors in the "green revolution" from 1961 to 2000*

Year	Adoption of Modern Varieties (million ha (% total growing area)) Wheat	Rice	Irrigation Area (million ha)	Fertilizer Use (million tons)	Tractors (million)	Total Cereal production (million tons)
1961**	0(0)	0(0)	87	2	0.2	309
1970	14 (20)	15 (20)	106	10	0.5	463
1980	39 (49)	55 (43)	129	29	2.0	618
1990	60 (70)	85 (65)	158	54	3.4	858
2000	70 (84)	100 (74)	175	70	4.8	962

* Adapted from Borlaug (1).

** Source: FAOSTAT (July 2002) and Borlaug's estimaled adoption (1) based on International Maize and Wheat Improvement Center (CIMMYT) and International Rice Research Institute (IRRI) data.

tes must restrict their sugar intake. Individuals with insufficient lactase enzyme experience diarrhea and bloating if they consume products that contain lactose (i.e., dairy products). Individuals with celiac disease (1-2% of the global population) must avoid gluten proteins from wheat, barley, and rye to prevent ongoing damage to their upper small intestine and potentially more serious autoimmunity, malnutrition, and/or cancer. A few individuals with IgE-mediated food allergies must avoid the foods that trigger their disease or risk experiencing severe anaphylaxis and potentially death. Other consumers with food allergies experience less severe symptoms. Many legume species must be cooked to inactivate lectins, protease, or amylase inhibitors and prevent malabsorption or pain and diarrhea. The FDA has required food labels for ingredients and nutrients for many years. However, passage of the Food Allergy Labeling and Consumer Protection Act (FALCPA) by the U.S. Congress in 2006 created additional regulations for labeling of allergens and celiac-eliciting food ingredients.

FDA Regulation of GM Plants

The FDA published a policy statement concerning the safety assessment of foods derived from GM crops (organisms) in 1992 (6), stating that recombinant DNA plants would be regulated within the existing Federal Food, Drug and Cosmetic Act. As stated, a GM plant having similar components (proteins, fats, oils, and carbohydrates) as a non-GM counterpart and no apparent risk from the inserted gene and expressed new protein is treated as a normal constituent and does not require special labeling. However, if there is any indication of a new risk, the novel ingredient must be treated as a food additive. The 1992 FDA policy (6) provided the EPA with lead-agency responsibility for GMOs with pesticidal proteins and the U.S. Department of Agriculture lead-agency responsibility in the case of GM meat or poultry. The policy clearly states that these agencies will work in a cooperative manner, with the FDA having ultimate authority on food safety. The primary focus of the policy guidelines is to determine whether a new protein presents a new potential risk of allergenicity or toxicity. In addition, the safety characteristics of the gene donor organism and the host organism (gene recipient) must be considered with regard to potential characteristics related to food safety.

Before gaining regulatory approval, developers of GMOs must supply study data verifying that their GMO products are safe. Based on the safety record and benefits provided by their approved GMO products, biotech companies are seeing GM seed sales rise, and the technology has gained wide acceptance by farmers. Of course, any agricultural practice has an impact on the environment, but in general GMOs are no more hazardous than their non-GM counterparts.

Evaluation and Regulation Based on Food Safety Principles

Before any GM plants were approved and released commercially in 1996, scientists from diverse disciplines were discussing opportunities, risks, and appropriate controls for the technology (2,13). The International Food Biotechnology Council (IFBC) was formed in 1988 and brought together "150 representatives of government agencies from 13 countries, industrial scientific organizations, professional societies, congressional-legislative staffs, public interest-consumer groups and academicians" from the food and biotechnology industries to draft a food safety document covering the general topic of the safety of foods derived from biotechnology (22). The full recommendations were published in a supplement to volume 12 of *Regulatory Toxicology and Pharmacology* (15). The consensus was that GM crops should be regulated within the legal and regulatory framework of foods and food additives that was developed over more than 80 years. The IFBC agreed that the primary task is to characterize the potential risk of a new protein or trait and to ensure that foods derived from the GMO are substantially equivalent to non-GM counterparts, at least within the range of commonly used nonGM varieties of the same species. The assessment strategy was refined further in scientific consultations, culminating with a *Codex Alimentarius* guideline published in 2003 and republished in 2009 (4).

This 2003 Codex document laid the foundation for regulation of GM products in the United States, Canada, Japan, and the international treaty members of the Codex Alimentarius Commission and was updated with minor revisions in 2009 (4). The guidelines recognize that all foods pose some risks for some individuals. The 4-6% of individuals worldwide with food allergies must avoid the specific foods that cause their reactions, while those without allergies can safely consume the same food (30). By the same token, individuals with celiac disease (1-2% of the world population) must avoid gluten proteins from wheat, barley, and rye (19,29). The primary concern for food developers is to avoid transferring a major allergen or potentially cross-reactive protein into a new food source.

Understanding the Technical Changes Introduced through Biotechnology

Although basic science courses provide knowledge on the structure of genetic material, reproduction, synthesis of proteins, and general physiology, many consumers do not understand the basic science behind biotechnology or that the products of genetic modification are predictable based on the nucleotide and protein sequences of the new trait. At the same time, the scientists who develop GMOs and the regulators who evaluate their safety must understand the subject in sufficient detail to ensure the proper functioning of a GMO and to understand the fidelity and nonrandom nature of living organisms. To bridge this gap, we as scientists must learn to communicate to consumers the concepts, reliability, and adequacy of the safety assessments used to ensure that GMOs are safe.

It is difficult for consumers to find simply stated information that describes the extensive premarket testing required for GMO products. Social and commercial news media sources frequently present polarized positions regarding the benefits, safety, and dangers of GMOs, often portraying reports of adverse effects as truthful and failing to mention the extensive literature and evidence supporting GMO safety.

It is important that consumers understand that unless they are intended to be different from their non-GM counterparts (e.g., as Golden Rice differs from regular rice) GMOs are the same in terms of their food safety and nutritional properties. As a result, the basic principles of food safety and food safety evaluation used for nonGM foods are fully capable of detecting any hazards associated with GM foods.

Characterizing the GMO DNA Insert and Function

The GMO developer must demonstrate appropriate function of the inserted gene, expression of the protein, and appropriate function of the specific new GMO. The DNA may be inserted

in many different regions of the host DNA, as long as it functions appropriately and does not disrupt other essential functions. Sometimes multiple copies are inserted into the chromosomes or insertion may occur at more than one location. Construction of the transformation vector and gene cassette must be defined and the method of insertion specified. The flanking sequence at the point of insertion is characterized to identify any unexpected or fusion proteins that might be expressed in the GMO that were not expressed in the non-GM host. Newer vectors and methods of controlling insertion are being developed and used, but it is important to realize that many processes are patented, and the techniques used in the 1990s are still scientifically acceptable for new products developed in 2014. Thus, if an independent scientist develops a new GM using older technology, it should be allowed if the product is proven safe and effective.

Characterizing the New Proteins

Consideration of potential risks is focused primarily on the safety of the new protein. The evaluation process begins by considering the possible history of safe (or unsafe) human exposure to the gene source. Extra testing may be required for genes taken from sources that are commonly allergenic or toxic, depending on whether there is information regarding the safety of the specific protein encoded by the gene. The amino acid sequence as expressed in the GMO must be verified, and the structure and function of the newly expressed protein are evaluated as well.

Evaluating Potential Allergenicity of GMOs

Few foods cause severe allergic reactions, and very few proteins within those foods are responsible for sensitization and elicitation. For example, there are four major allergenic proteins found in peanuts, and these proteins are abundant. Peanut allergy is thought to cause ~50–80 deaths per year in the United States in consumers who are allergic and unsuccessful in avoiding peanuts in the foods they consume. Soybean, which is estimated to cause less than one fatal allergic reaction per year in the United States, contains eight or nine moderately allergenic proteins in its seeds.

It is important to prevent the transfer of an allergenic protein from food airway, contact, or injection sources into a new food that an allergic consumer would not recognize as containing the allergen. For instance, transferring the allergenic 2S albumin Ara h 2 from peanut into rice would put many people who are allergic to peanut at risk of severe reactions. It is relatively easy, however, to identify most of the important risks of transferring food allergens if a few simple steps are followed. This was demonstrated in 1996 (26) by the evaluation of the protein from a Brazil nut gene that was transferred into soybean to increase its nutritional properties for agricultural animals—a case where substantial risk was possible. The tests were performed because the source of the gene is known to cause allergic reactions in some individuals. Today, more allergens have been identified and added to databases such as AllergenOnline, and a similar protein would have been flagged as a likely allergen requiring serum IgE testing due to high sequence identity matches to other allergenic 2S albumins (described below).

The steps required for the assessment of GM crop allergenicity have often been misinterpreted, or the risks have been overemphasized (11). Undoubtedly the most important step is a bioinformatics search to compare the sequence to those of known allergens using a well-characterized allergen database (10). AllergenOnline (also termed the FARRP database by some; http://www.AllergenOnline.org) currently is the only peer-reviewed, sequence searchable database available for public use. It is updated annually, and version 14 (released January 2014) includes 1,706 sequences in 645 taxonomic groups. The sequences are selected based on criteria to evaluate data published to demonstrate IgE binding, using clinically defined serum donors and test method criteria. Sequences in the NCBI Protein database — http://www.ncbi.nlm.nih.gov/guide/proteins — may also be used for comparison using key word limits (e.g., allerg*, allergen, or allergenicity), but the user is then responsible for evaluating the relevance of any match: there are more than 52,000 sequences in the database that are associated with the key word "allergen" (as of April 26, 2014), and for many, there is no proof of IgE binding or causing reactions. The most informative search is a full-length alignment, and if the new GM protein matches a known allergen with >50% identity and a very small *E* score, the alignment is likely to show cross-reactive IgE binding and possibly shared allergic elicitation. However, allergens are not equal in potency or frequency of elicitation. In addition, the Codex guidelines (4) recommend searching for matches of >35% identity over any alignment of 80 or more amino acids using either the FASTA or BLASTP programs (4). In addition, many countries expect a short identity match comparison that looks for segments of eight contiguous amino acids that match any allergen. However, there are a number of publications that demonstrate a short segment match is not predictive (32).

If the GM protein aligns with an allergen at >35% identity over 80 or more amino acids, serum IgE binding tests would normally be required, using sera from donors that are clinically defined with the appropriate allergies and validated methods (9,11). Some proteins identified in AllergenOnline or in other publications rarely cause any allergic reaction. It will prove impossible to find qualified donors for such proteins, but for them the risk of allergic reaction to the GM protein is likely to be extremely low. Additional considerations include the need to use sera from subjects with other allergies as negative control donors to ensure that IgE binding is specific and also to use positive and negative control antigens (9). If binding is observed, it is usually informative to perform specific inhibition tests to validate the specificity of binding. If the GMO developer wants to proceed with a product that has some positive binding, it is necessary to evaluate the biological relevance of the binding using basophil activation or histamine release. Alternatively, in vivo skin prick tests or other challenges would be appropriate, although it is essential to consider whether the potential risk to the patients is warranted (11).

Additional steps in the Codex guidelines (4) are more relevant for determining whether a new protein might become an allergen based on the characteristics of many known food allergens. Or alternatively, they may be used in considering appropriate risk assessment and mitigation steps if the protein is determined to be an allergen after approval. The stability of the protein in pepsin and under heating conditions may be useful in the initial evaluation because many major food allergens are relatively abundant and stable in pepsin at pH 2. Stability in heat means the protein maintains its three-dimensional form and function when cooked at "normal" cooking temperatures. Many major food allergens are also quite abundant in a food. Therefore,

pepsin and heat-stable, abundant proteins may pose a risk of sensitization in the future, although there are a number of very stable and abundant proteins that do not cause food allergies. It would be extremely useful to have a predictive animal model or cell culture system (e.g., dendritic cells, T cells, and B cells) for accurate evaluation of the sensitizing potential of novel proteins. However, no animal model, cell culture method, complex protease digestion protocol, or computer prediction modeling has yet been demonstrated to accurately predict the risk of sensitization for humans (20,21).

Evaluating Potential Toxicity of GMOs

The Codex guidelines call for evaluation of the potential toxicity of a protein (4). In their review, Delaney et al. (5) provide an interesting model for safety evaluation for potential toxicity. It is based on the source of the gene (i.e., whether it is likely to be toxic or not) and a bioinformatics match to known toxic proteins or enzymes that make toxic metabolites. A history of safe use or human exposure is a key component of a toxicity evaluation. There are very few proteins that are toxic when ingested, such as botulinum and ricin, which are highly toxic. Even proteins with fairly high identity matches to these proteins are not known to be toxic (unpublished data). There are many "toxic" proteins from stinging insects, snakes, and other organisms, but many of them are unlikely to cause toxicity if consumed at low concentrations.

A comparison of the GM protein by BLASTP to the NCBI protein database using key word limits "toxic" or "toxin" will identify significant matches to toxic proteins. There are no absolute criteria for this search, so it is important to use relative comparisons if a significant match is found (e.g., >50% identity over most of the length of the protein, with an *E* score smaller than 1e-15). In this case a BLASTP search using the GM protein with no key word might identify proteins with a history of safe use and high identity to the GM protein. A search comparing the matched toxin to other proteins in the NCBI database also would be instructive. If the gene is from a toxic sequence source and matches a toxin with modest identity, then specific tests should be performed based on the toxic characteristics of the protein (e.g., neurotoxin for many snake and spider venoms or liver toxicity for some mycotoxins). Some countries require an acute mouse gavage with the protein if the GM protein is insecticidal (e.g., EPA) through oral administration at high dose followed by observation of clinical signs for 14 days before sampling for blood chemistry. The mice are then killed, and their organs are analyzed for differences in weight compared with control mice and for gross pathology and, when appropriate, histopathology following good laboratory practices.

Some governments require a 90 day, rat whole-feeding study for most GM crop products. In this case, groups of rats are fed diets with a high inclusion rate of the GM crop material and identical doses of non-GM crop material from genetically similar varieties. Additional commercial non-GM varieties are used with groups of rats to evaluate minor statistical differences that might be due to chance. This is not a true toxicity study, but a nutritional equivalence study.

There is no need to perform chronic studies or multigeneration studies unless there is a scientifically justified rationale to suggest the GM product or protein is likely to have long-term effects. In my opinion, the currently approved GM products (109 in the United States) do not have characteristics that would warrant such tests. In any test that is intended to identify potential toxicity, there must either be a history that the test can predict a toxic effect in humans or an animal species of concern, or positive and negative control test articles must be included in the study to evaluate the biological relevance of any noted difference(s).

Analysis of Nutritional Adequacy

Specific foods are consumed to supply nutrients. Humans are omnivores and can develop and survive on highly varied diets. However, we generally are concerned with feeding nutritionally adequate diets to agricultural species (e.g., chickens, cows, fish, and pigs) that have restricted diets. Therefore, it is important to ensure that the nutritional properties of a GMO are similar to those of non-GM varieties intended for similar use. In most cases, simple proximate analysis is all that is necessary, using samples from multiple field trial sites. However, for specific crops there may be specific nutrients (e.g., vitamins, minerals, and fatty acids) or antinutrients (e.g., phytate, lectins, amylase, or protease inhibitors) that are monitored to verify "safety." If the new GM protein is an enzyme that is active in the plant, it is important to evaluate specific metabolites based on the functional properties of the enzyme and the metabolic pathways in the host (gene recipient). For example, Monsanto evaluated the impact of inserting the enzyme CP4 EPSPS in its Roundup Ready soybean because the enzyme is known to produce metabolites that lead to the formation of aromatic amino acids, flavonoids, and other aromatic amino acids or isoflavones. No significant differences were found between non-GM and herbicide-tolerant Roundup Ready soybeans (27,34). Some future GM crops are intended to have changes in their nutrient profIles. For example, Golden Rice 2 (GR2) expresses high levels of β-carotene due to the insertion of two genes that express enzymes essential for the synthesis of β-carotene (28). Non-GM rice does not normally express β-carotene (also called provitamin A). To make a health claim that GR2 has the potential to provide sufficient provitamin A, the developers had to demonstrate a substantial accumulation of the compound and associated α-carotene in the rice grain (28).

Conclusions

To date, there is no proof of harm to humans or farm animals from consumption of approved GM varieties of plants. To maximize efficiency and minimize costs, the safety evaluation process for food and feed should be the same in all countries. It is unfortunate that there isn't a mechanism for global approval because the current system leads to long delays in global trade of commodities and finished food products. The process also adds costs when reports and, in some cases, duplicate studies are performed. It is also clear that generically labeling foods as "GMO" will not provide any relevant health benefit, because any possible harm will be product specific, and the dose and, thus, exposure will vary markedly between products. Labeling only provides a way to discriminate against a technology with many important benefits. To combat unsubstantiated concerns, it is clear that scientists need to develop more effective methods of communicating with the public to provide assurances about the safety of foods produced from approved GM varieties.

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