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REVIEW



Twenty-eight years of GM Food and feed without harm: why not accept them?

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ABSTRACT

Since the first genetically engineered or modified crops or organisms (GMO) were approved for commercial production in 1995, no new GMO has been proven to be a hazard or cause harm to human consumers. These modifications have improved crop efficiency, reduced losses to insect pests, reduced losses to viral and microbial plant pathogens and improved drought tolerance. A few have focused on nutritional improvements producing beta carotene in Golden Rice. Regulators in the United States and countries signing the CODEX Alimentarius and Cartagena Biosafety agreements have evaluated human and animal food safety considering potential risks of allergenicity, toxicity, nutritional and anti-nutritional risks. They consider risks for non-target organisms and the environment. There are no cases where post-market surveillance has uncovered harm to consumers or the environment including potential transfer of DNA from the GMO to non-target organisms. In fact, many GMOs have helped improve production, yield and reduced risks from chemical insecticides or fungicides. Yet there are generic calls to label foods containing any genetic modification as a GMO and refusing to allow GM events to be labeled as organic. Many African countries have accepted the Cartagena Protocol as a tool to keep GM events out of their countries while facing food insecurity. The rationale for those restrictions are not rational. Other issues related to genetic diversity, seed production and environmental safety must be addressed. What can be done to increase acceptance of safe and nutritious foods as the population increases, land for cultivation is reduced and energy costs soar?

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Introduction

I worked on the safety assessment of genetically engineered or genetically modified crops at Monsanto Company from August 1997 until I moved to the University of Nebraska–Lincoln in 2004 as a Research Professor. I was involved as a Non-Governmental Organization representative at the CODEX Alimentarius meeting in Vancouver Canada September 9–12, 2001 where the Allergenicity Guideline that was approved in 2003 was drafted (CODEX, 2003¹ and²). At UNL, we started the www.AllergenOnline.org database in 2005³ with financial support from major plant biotech companies. We became fully independent in 2019 as many of the biotech companies dropped financial support between 2017 and 2019. My work at Monsanto and after at the University took me to India 40 times discussing food safety and allergenicity with the Department of Biotechnology and I continued providing some advice until long

after the Indian Council of Medical Research adopted the CODEX guideline steps for assessing potential allergenicity of biotechnology products in 2008. Regulatory agencies, biotechnology companies and academic scientists have invested an enormous amount of scientific work and funding in efforts to evaluating potential risks and have developed methods to ensure minimal risks for consumers and the environment from biotech products (GMOs). Each GM event is evaluated extensively before being used in commercial production. Some extra information demanded by the European Food Safety Authority and various governmental regulators is academically interesting, but results are often not relevant for assessing safety. Now the same questions are being asked for novel foods that are being developed from other organisms including fungi, algal species and bacteria and the results may block entrance of new foods from the market. A good example relates to evaluating

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potential risks of food allergy as demonstrated by Abdelmoteleb et al.⁴

Safety evaluations of GMOs started long before the first biotech crops were approved and sold in 1994. Paul Berg and other top scientists who were developing biotechnology medical and industrial products raised questions and organized the year moratorium on research with recombinant DNA species and the Asilomar conference in 1973 discussed many possible concerns and transfer of DNA into various microbes. The 1-year moratorium on DNA splicing and transfer in 1973–1974 was to provide detailed discussion and consideration of potential risks and how to minimize them. One advancement was the adoption of the *Escherichia coli* K12 strain, which is unable to grow outside of the laboratory as the only bacterial strain that could be used for construction and amplification of recombinant DNA.^{5,6} In 1986, the US Government published their Coordinated Framework for Regulation of Biotechnology as described in the Federal Register following academic conferences in the United States⁷ as outlined by the White House Office of Science and Technology Policy (website); then the US FDA guidance on safety assessment of genetically modified crops. The FDA formally presented the process in the Federal Register in 1992. Global communications and treaties including the Convention on Biological Diversity (1993–2023) www.cbd.int/brc/, which includes plant genetic resources in Agriculture in became operative with a database about Living modified organisms (CBD 2004⁸), under the Cartagena Protocol for Protection of the Environment is based on Living Modified Organisms, but did not address food safety except in a short paragraph stating that food safety should be evaluated. The purpose of the Cartagena Protocol is to help ensure that something like Kudzu vine (Japanese arrowroot or Chinese arrowroot) the invasive plant that covered much of the Southern United States after being introduced in 1876 and used initially to stop soil erosion along roads and railroads. It strangles trees and native plants and has been noted as a major problem since 1949. Another example of a plant to control is short ragweed (*Ambrosia artemisiifolia*) that has spread from North America across much of the temperate regions of Europe and Asia and causes significant airway allergy and asthma from pollen proteins. Controlling invasive

species is important. However, the food and feed crops that have been changed by biotechnology, such as soybean, maize and cotton, require human agricultural practices for them to grow, plowing and weeding to prevent native crops from crowding the food and feed crops.

The food safety evaluations necessary for GM crops focus on realistic risks and are outlined clearly in the CODEX Alimentarius Guideline that was drafted following many consultations and much debate in the early 1990s and beyond. Issues of evaluating potential food allergenicity, toxicity and nutritional properties for human health were considered through the United Nations Food and Agricultural Organization and the World Health Organizations FAO/WHO (in 1991, 1996, 2000, 2001). The CODEX Alimentarius Commission held evaluations in 2001 to decide what Food Code requirements should be considered for genetically engineered crops. Their output was finalized by country representative votes in 2003. The CODEX guideline remains in effect in 2023 and informs the development of country-specific processes for food safety.

Since the Chinese government has been wary of adopting GM technology a joint Academy of Sciences meeting was organized to help build the science-based regulations since China represented nearly 25% of the global population and continued to import commodity grains and seeds. The Chinese and United States Academies of Science held a joint meeting in Wuhan, China and published a series of papers in Chinese and English about development of processes for GMOs, specific GMOs and safety considerations (Wuhan, 2014⁹) (Table 1). Certainly, while each country has the right to their own regulations, the CODEX Alimentarius Guideline (2003 and 2009) provided a peer-reviewed science-based recommendation for evaluating genetic stability, potential allergenicity, toxicity and nutritional equivalence of crops modified through biotechnology. The process starts with evaluation of the history of safety from peer-reviewed publications of the organism and gene donors and proposes specific tests to consider potential food allergy, toxicity and impacts on nutrition. Countries that signed CODEX are supposed to follow those recommendations or risk an action by the World Trade Organization (WTO) if

they have not developed science-based guidelines that are followed. While the Convention on Biodiversity and finally the Cartagena Protocol (Cartagena, 2003¹⁰) are intended to protect the environment, evaluation of human food and animal feed safety is covered by CODEX and by guidelines under the Organization of Economic Community Developments (OECD). The CODEX guideline (2003 and 2009) is very similar to recommendations outlined by the US coordinated framework.⁷

A similar conference of international and national scientists might have helped India move forward with science-based evaluations for food crops. Although scientific meetings held by the Department of Biotechnology and AgBios have been performed in India, the government has not adopted other food crops. They did accept insect-resistant cotton from Monsanto, Bollgard I in 2005, and Bollgard II soon after and oil from cottonseed is used in food. But approvals of food crops have been lacking as described for insect resistant eggplant or brinjal, with the same GM construct as Bollgard I. Decisions about GM food crops seem to have been stifled by politics and fear propagated by activists including Vandana Shiva, who claims to be in favor of organic farming which cannot

possibly feed the 1.4 billion Indians and by Suman Sahai of Gene Campaign who has been active against any industrial agriculture. Both have been successful at spreading misinformation about GM crop safety since the early 2000s. The South Asia Biosafety Program has held numerous science-based workshops in India and Bangladesh since the early 2000's to discuss and train scientists on safety of biotechnology and agricultural practices. At one workshop that I attended in New Delhi before 2008, Suman Sahai presented information suggesting that the biotechnology crops like Bollgard® cotton, that reduce the need for chemical pesticides, were responsible for social issues and that they were not tested for safety. As an invited speaker she refused to take questions after her talk and did not stay for discussions of scientific data of all speakers. I presented the safety assessment process followed by Monsanto for Bollgard cotton. The discussions then and now are on social media, without scientific discussions or verifiable information. The contrast between India and Bangladesh shows markedly different choices and outcomes that impact farmers and food suppliers as well as consumers.

The potential risks posed by GMOs are not different from risks posed by any foods that have been historically consumed. Primary risks differ

Table 1. The conference in Wuhan produced a number of papers with Chinese and English translations from all experts that were published in volume 33(6) of the journal of Huazhong agricultural university (2014) as shown below. The articles were originally open access but are not available on their website any longer. If you are interested in any of them, e-mail rgoodman2@unl.edu for PDF copies.

Authors	pages	Title
Delmer, Deborah ¹¹	1–10	GM crops and food security
Zhang, Qi-fa ¹²	11–16	Demands for green technologies in future plant breeding
Brookes, Graham, Barfoot, Peter ¹³	17–23	Key global economic and environmental impacts of genetically modified (GM) crop use 1996–2012
Raven, Peter H ¹⁴	24–31	Global perspective: GM crops and biodiversity
Newell-McGloughlin, Martina ¹⁵	32–39	Future directions, development and application of GM crops in the USA
Nepomuceno, Alexandre L, Lopes, Mauricio A., Finardi-Filho F, Coelho, MVS, Fuganti-Pagliarini R ¹⁶	40–45	Biosafety legislation and the use of GM crops in Brazil
Wesseler, Justus, Drabik, Dusan ¹⁷	46–53	The situation for genetically modified crops in Europe
Zehr, Usha B ¹⁸	54–58	GM crops in India
Obokoh, Nompumelelo H. ¹⁹	59–68	The status of GM crops in Sub-Saharan Africa
Dubock, Adrian ²⁰	69–84	The present status of Golden Rice
Goodman, Richard E ²¹	85–114	Biosafety: evaluation and regulation of genetically modified (GM) crops in the United States
Wu, Kong Ming ²²	115–117	Environmental safety evaluation and risk management of GM crops in China
Chen, Xiaoya, Yang, Changqing, Jia, Hepeng	118–120	Issues confronting GMO crops in China
Lynas, Mark ²³	121–122	Why GMOs are green-biotech crops to benefit the environment and reduce poverty
Chrispeels, Maarten J. ²⁴	123–136	Global production and consumption of genetically engineered crops

from species to species and at least partly between individual consumers. Potential allergenicity, toxicity, anti-nutrients and nutrients are and should remain the primary focus of safety assessments of GMOs, conventional and organic crops. While social media and mainstream media carry occasional stories of reported harm from GMOs, scientific evaluation of claims have not verified the suggested harms. Food labels of “GMO” are taken as a sign of risk, while an “Organic” label is seen as a marker of safety. Yet the labels are not accurate in demonstrating harm or safety. Both can mean little or no added chemical pesticides in the field or as residues on crops and neither is inherently different in terms of good soil and water quality protection. The labels are about farming practices and possibly efficiency. There is no measure of food safety linked to organic foods, and they are not evaluated for safety like GMOs are. Each GMO event (species and gene insert) product has been through an evaluation process to consider risks of allergy, toxicity and nutritional equivalence and gene stability. Some of the rules for organic could be used to describe a GMO. If the farming practices are done correctly, products from organic, conventional and GMOs farming should be safe for human consumption and the environment. Generally, products produced by either organic or GM should be safe and farming practices should lead to a sustainable environment.²⁵ GMOs have been placed in the conventional food category in the United States through political pressure, that means labeling laws for organic do not allow a GMO to be labeled as organic. Interestingly, microbial pesticides with *Bacillus thuringiensis*, which include about 5,000 bacterial genes, may be used on a crop that can be harvested and the food called organic. But if one gene is inserted from *Bacillus thuringiensis*, such as Cry 1Ab in MON810 maize, it cannot be used to produce food that might be labeled as organic. Both products can reduce chemical pesticide on maize or corn.

Food Labeling Laws

In most countries, food labeling laws are intended to help consumers make safe choices in purchasing and using foods. People with Celiac Disease (CeD)

need to avoid gluten proteins in wheat and near wheat relatives (barley rye and hybrids) to remain symptom free. They rely on food labels to understand safety. There are many different gluten (glutenin and gliadin) proteins that can trigger pathology of Celiac Disease; thus consumers look for information about ingredients from wheat, barley, rye and relatives. The individual proteins cannot be labeled. There is a threshold of 20 ppm gluten for labeling foods as gluten free.²⁶

There are no threshold doses for labeling allergens as there are for gluten. A conundrum for some is that wheat is considered a major IgE allergen, requiring labeling. Some products are labeled gluten free if they have less than 20 ppm gluten, but they must be labeled as containing wheat because the food can be a risk of IgE mediated food allergy for those allergic to wheat although the product may not contain gluten.

Foods that are packaged and contain proteins from major allergenic food sources must be labeled so that consumers can avoid their allergen. Labeling rules in the United States demand clear statement of ingredients, often in a “contains” statement for the nine priority species: peanut, tree nuts, fish and crustacean shellfish, wheat, cow’s milk, and eggs as well as sesame seeds. Canada has added mustard and sulfites. Europe requires labeling for 14 priority food ingredients including sulfites, crustacean and molluscan species, mustard, and lupine. Allergy studies show that it is the major proteins in those sources that cause food allergies, but it is the whole food that is used as may be used and that is what allergic consumers recognize as their allergen. Allergic consumers rarely know what allergenic protein causes their IgE antibody-related allergic reactions, and their diagnosis is rarely that specific. And in general foods are not made with markedly different allergen content except for specific concentrates of isolates which are still not highly purified. People who accidentally consume their allergenic sources can become very ill and a few people die every year due to severe anaphylactic responses to proteins from their allergenic food source, usually from peanut, a few tree nuts, milk or egg proteins. The point of labeling is to give the consumer the information needed to ensure their ability to avoid their allergens to ensure safety. The responsibilities are

shared between consumers, their allergists, regulators and food producers. For the producer, including the GMO developer, the primary safety question is whether they have transferred an allergen or a protein nearly identical to an allergenic protein into a food that is not labeled but that might cause those with existing allergies to have an unexpected reaction.

Genetic engineering or genetic modification is a process of transferring DNA into a different organism. There is nothing inherent to the DNA or the method of transfer that causes risk of disease. Therefore, labeling a food as containing a GMO does not provide any safety information. It only allows discrimination based on a philosophical idea, not on safety. The argument is that consumers have the “right to know” what is in their food. But know what? GMO does not tell the consumer anything about the gene donor, the host product, the proteins that may be new in that product or the purpose of the GM event and certainly nothing about risks. However, if the GMO or a novel food contained a major allergen from a major allergenic source, the GMO must be labeled with the specific risk factor, the allergen source or a protein that is likely to cause allergic cross-reactivity to one of the priority allergens.

Governments and food companies work together, to inform the consumer about things that may be of religious or psychological interest, helpful or harmful for health (contains sugar, alcohol, allergens, glutens, vegetarian, vegan, meat, kosher, halal). But to a great degree labeling is about selling a product. In industrialized countries there are laws about mislabeling or lack of labeling for gluten (if less than 20 ppm gluten it is OK, if higher in concentration they must be labeled as containing gluten or from wheat or their gluten source). For allergens, there are no thresholds of concentrations for labeling. However, there are studies demonstrating on an individual basis and a population basis that there are thresholds for total protein from major allergenic foods but not individual allergens, with peanut being the most tested by clinical food challenge studies.²⁷ The minimum eliciting dose for foods was measured as dose of protein from specific foods that cause objective symptoms (visible to a medical person) of hives, fever, asthma, vomiting, or diarrhea during

a measured dose test that includes blinding the consumer to the sample. In a test of up to 3,000 subjects peanut allergic subjects a clear population safety dose was determined. But in this study testing reactivity to a number of allergens, at least 66 subjects allergic to any one food was tested from a total of 238 subjects.²⁷ Additional studies were reviewed and the effective dose (ED_{05} , where 5% of highly allergic subjects would react was calculated). In Table V of the others, Turner et al.²⁷ report. The ED_{05} values are listed in mg specific total protein from the allergenic source and were around 2 mg for most foods, but for wheat it was 6 mg, for fish it was 12 mg, soybean 10 mg, and shrimp 280 mg. However, no government has adopted those levels for the purpose of food recalls if they are not labeled with the specific major allergen. The point is that there are hazards for specifically allergic people, but thresholds differ among individual consumers and labeling is demanded for food safety to protect the most highly allergic people. Since food manufacturing is complex, going from the farm (source) to the consumer's plate has many processes in production or cooking that could result in mistakes and contamination or inactivation. There are arguments about precautionary labeling stating a food “may contain” an allergen, but not as an intentional ingredient, in processed foods (PAL) as described by others, Turner et al.²⁷

Development of GMOs

Between 1994 and July 2023, several genetically engineered crops and a few genetically engineered animals were developed and approved for food use in at least one country (ISAAA.org GM database). Now there are 386 events (trait and crop or animal species) of genetically engineered (GE or GMOs) approved for food use in at least one country.

The definition of a GMO is any organism that has had direct transfer of a gene (DNA) through biotechnology from a different species, and the DNA is incorporated into the recipient and becomes an inheritable part of the organism. The method of the initial introduction of DNA as described in the ISAAA.org website (www.isaaa.org/gmapprovaldata) for most crops was by *Agrobacterium tumefaciens*-mediated transformation. A plasmid of the plant disease vector *A. tumefaciens* was modified to

transfer specific segments of DNA from bacterial and plant sources by the modified infectious bacterial vector without causing plant disease. The second most common method of initial DNA transfer was by particle bombardment of DNA on metal particles using a gene gun. In addition, once the DNA is stably transferred and tested, one event can be transferred into other varieties of the same plant or animal by traditional breeding. A few other methods of transferring DNA have been accomplished including electroporation, aerosol injection and chemically mediated transformation.

The 25 crops that have been transformed and approved for food use include alfalfa, apple, canola, beans, chicory, cotton, cowpea, eggplant, eucalyptus, flax, maize, melon, papaya, pineapple, plum, potato, rice, safflower, soybean, squash, sugar beet, sugarcane, sweet pepper, tomato and wheat (www.isaaa.org/gmapprovaldatabase/). Not all of them are produced commercially or used in foods today. Many commercial species that have been developed and approved for cultivation somewhere and used for food include canola, cotton, maize, potato and soybean. The number of events approved by 2023 in various countries and accepted for food use include the United States (217), Japan (196), Canada (192), South Korea (170), Taiwan (150), Australia (144), European Union (116), Brazil (112), New Zealand (114), Argentina (80), China (77), South Africa (72), Singapore (39), Nigeria (29), Russia (28), Vietnam (22), Thailand (15), and India (11). The total number of countries that have approved at least one GMO for food use is 45. Some countries such as Japan do not allow cultivation of GM crops but do allow importation and use for food or feed. In the European Union only Spain and Portugal allow cultivation of only one maize variety. Romania used to allow cultivation of the same variety, while other countries have yet to approve GM cultivation. However, most EU countries do import commodities of specific GM events for animal feed or human food use. Before importation, the countries require data demonstrating safety and characterizing the specific GM event.

The first GM species approved for food use were for cotton, maize, soybean and tomato in 1994–1995. Progress and milestones are outlined in the US Government Food and Drug Administration website

www.fda.gov/food/agricultural-biotechnology/. See also www.fda.gov/feedyourmind.

During the past 15 years, the growth in development and approvals has been rapid with most products developed by international biotechnology companies, or through collaboration of academics or national companies in India and China. The AATF (African Agricultural Technology Foundation) through worked CIMMYT (www.cimmyt.org/) and the CSIRO (Australia's National Science Agency) to developed different insect-resistant cowpeas (*Vigna unguiculata*) using genes from *Bacillus thuringiensis* (Cry1Ab and now Cry2Aa) for moth caterpillar pests including the Marucid moth (*Maruca vitrata*). Farmers in Nigeria have been able to use Cry1Ab GM cowpeas in 2021 and those in Ghana should gain access to those varieties in 2023. A researcher at CSIRO, Thomas J Higgins, developed cowpeas resistant to a seed storage beetle Bruchid beetle (*Callosobruchus maculatus*) by transferring the alpha-amylase inhibitor gene from common bean (*Phaseolus vulgaris*). Early test plots in 2005 demonstrated the probable value of the GM variety. Further development and characterization are nearly complete for submission of data to regulators in Ghana and Nigeria. In those cases, scientists including biotechnologists, agronomists and plant breeders collaborated to ensure the products are stable and are in plant varieties will be productive in the target countries (Nigeria and Ghana). The same pests cause crop losses in several Sub-Saharan countries including Burkina Faso, Mali, Ghana, Niger and Nigeria. Hopefully, these events or similar ones will be approved for use in those countries as cowpea provides good digestible proteins in a drought tolerant crop.

The time required to transform a plant, to test safety and efficacy and ensure the right varieties include the trait and are available for farmers often more than 12 years. In Ghana and several African countries, the laws and rules have changed from adoption to rejection and now hopefully to pathways that are based on science. Such changes are often based on political decisions that cause uncertainties for developers and seed companies.

In some cases, extensive tests of a GM crop have identified problems in a transgenic variety that can be solved by selection of the right event and by

selective breeding for unrelated genes. Golden Rice in the Philippines was started by a collaboration of two European scientists (Ingo Potrykus of Switzerland and Peter Beyer of Freiburg Germany). A major biotechnology company, Syngenta, gave the gene sequence and did initial transformations. Many scientists contributed over three decades to the development and testing of specific events. The final responsibility is held by the International Rice Research Institute in the Philippines (www.irri.org/golden-rice-faqs). There were changes in donor genes during development and unfortunately the selected line that underwent many field trials was inserted in an important gene for root development. It took more than two years to recognize the problem before another insertion event was chosen that was not in the root promoter but was efficacious and could be carried forward. Full characterization and testing allowed the GR2E event to be approved in the Philippines in 2019 and in Bangladesh in 2021. The GR2E seeds are being released to many farmers in the Philippines in 2023.

Development of most of the GM crops is driven by a need to improve production of the crops through protection against insect predation, or resistance to plant disease (papaya ring spot virus, viruses in potato, bacteria in plum trees and bananas) and environmental challenges including drought. TELA maize was developed initially as WEMA (Water Efficient Maize for Africa) that started in 2008. It was funded in part by the Bill & Melinda Gates foundation, the Howard G. Buffet Foundation and U.S. Agency for International Development (USAID), with drought tolerance achieved through a GM event by insertion of a cold-tolerance gene. Conventional varieties that are naturally drought tolerant were also used by breeding and hybridization. The current TELA products are hybrid varieties with drought tolerance and insect resistance through addition of different GM varieties. It has been supported in part by Monsanto, now Bayer and by CIMMYT working through licensing with AATF. Various combinations of genes are being field tested and released in Nigeria and Kenya in 2022. Testing of the GM events have followed the CODEX Guidelines and costs to farmers who receive the seeds are held to a minimum with plant rights protected under

African laws for TELA® maize hybrids. Nigeria has approved TELA maize and Kenya seems likely to approve TELA maize following 2023 field testing.

Interesting and helpful nutritional enhancements are being developed as seen with Golden Rice. A more complex GM event is described for *Brassica napus* or Argentine canola by Nuseed Pty Ltd with transformation and initial characterization done at CSIRO in Australia. The plant was designed to produce DHA fatty acid (docosahexaenoic acid) in canola to replace fish oil Omega 3 ingredients for improving cardiovascular health.²⁸ A combination of seven genes were needed to produce DHA providing a new metabolic pathway in canola. The product has now been approved in Australia Canada, New Zealand and the United States with food safety approvals following study evaluations.²⁹

Differences in approvals and processes between countries for approval of GMOs can be illustrated by insect resistant eggplant or brinjal. The GM plant was developed by MAHYCO, Maharashtra Hybrid seed Company in India. They introduced the same Cry1Ac gene from *Bacillus thuringiensis* and the same construct used to produce Bollgard I cotton that was developed by Monsanto. Brinjal, *Solanum melongena* submission by MAHYCO was in 2008 to the government of India. However, the submission was rejected after approvals by the RCGM (Review Committee on Genetic Manipulation) and GEAC (Genetic Engineering Appraisal Committee) after evaluation and discussions. However, it was rejected by the Minister of Environment in India in 2010 as some parts of the submission left questions, but after committee approvals the Minister was adamant in rejection.³⁰ In 2012, the government of Bangladesh allowed field trials of the same GM event and in 2013 accepted four GM plant varieties that were bred from the original transformed event. Those are now approved and are being grown by many farmers in Bangladesh. The same varieties of eggplant were approved in the Philippines in 2021 for food and for cultivation in 2022 with approvals in Bangladesh.^{31,32} While the chemical pesticides used in India to control the moth should be safe if used correctly, it is likely that there are pesticide residues commonly on the fruits in India and the pesticides also are common chemical contaminants for soil and water in India.

Agriculture in Africa is different from that in North America, Europe, Australia, and China. Some productivity could be gained, and quality could be maintained by accepting some GM Crops that are developed in Africa or in other countries. TELA maize could reduce maize crop losses to drought, but also to insects, including Fall Armyworm (*Spodoptera frugiperda*) that was accidentally introduced into Sub-Saharan Africa from the Americas before 2016. The moths rapidly spread across Africa and Asia and continue to cause crop losses in maize, and in some other crops. While some chemical pesticides can kill the caterpillars or adults, small-holder farmers often do not have access to those pesticides or they cannot afford them. Some of those chemicals are persistent or hazardous in ground water. Scouting for early infestation is hard and early control is important in stopping infestations. TELA maize, MON810 and a few other GM events could limit losses. Nigeria and Kenya are about to start using some of those events which should help stabilize production with reduced crop loss to this pest.

Late Blight Resistant potatoes were developed by the International Potato Center by introducing resistance genes from wild potato relatives. This *Phytophthora* organism caused the Irish Potato Famine in 1845–1849 and continues to cause damage and losses of potatoes and other solanaceous crops. The GM potatoes are meant for production in Uganda and Kenya, and they have been in field trials over five years to demonstrate protection from *Phytophthora infestans* they must go through the normal GM evaluation process.

Control of Brown Streak Virus in cassava in Africa has been intensively studied since the 1930s but still in 2022 permanent control of the virus is not available although several GM events have been tried.³³ Properties specific to the regional viruses are required.

Bacterial blight resistance in bananas was achieved by Leena Tripathi and colleagues by transferring genes of two pepper defensins from commonly consumed peppers into local banana varieties. Safety testing for and efficacy seems good,³⁴ but since it is a GM variety, it would require extensive testing that is expensive and time-consuming. Therefore, Tripathi and colleagues are now using gene editing to produce effective resistance to the same bacteria.³⁵

Safety Assessment of GMOs

In the United States, the FDA published guidance on the assessment of genetically engineered crops in 1992 that provided guidance on requirements from the FDA.³⁶ Developers of any crop or animal GMO must maintain records and provide data to regulators in the United States (FDA Center for Food Safety and Nutrition) and/or USDA APHIS (animal and plant health inspection service).³⁷ If commodities or foods containing a GMO are to be exported to other countries, those countries have regulatory agencies that can require the same or additional data (Health Canada, Food Standards Australia New Zealand or FSANZ, European Food Safety Authority (EFSA), Food Standards Agency of the UK, Ministry of Health, Labour and Welfare or MHLW in Japan, and similar agencies in any importing country. If a GMO was developed in a country outside of the United States, the developer would be required to submit similar data to US regulators. Some countries such as Canada and Australia/New Zealand are sharing GM safety data since 2019 to improve efficiency and reduce costs. Few other countries share comparable data, partly because of proprietary and ownership issues. In general, each country has guidelines on confidentiality of that data.

Cartagena Protocol for Environmental Safety

Although I think countries that rely on the Cartagena Protocol for controlling LMOs are substituting the concept of GMO with LMO and increasing the complexity of evaluations. One aspect of the Cartagena Protocol that does have value is the requirement to maintain the Biosafety Clearing house of information required by that agreement for those countries that signed the agreement does require some information that is relevant for overall food and feed safety. For instance, the PDF from Japan on insect resistant MON810 with the Cry1Ab gene for lepidopteran resistance lists the source of the gene, the event, places the event is accepted and information about acceptance.

Overall, the Cartagena Protocol requires evaluation of potential weediness and expected environmental impacts of an LMO (seed or reproducible tissue such as a potato tuber) and emphasis is on

impacts if the organism is released and allowed to grow after import. Some records in the clearing house are relevant to food safety as far as reporting the inserted gene, control elements and tests are described for some organisms, possibly from the European Commission and may include elements such as the CaMV 35S promoter, the marker gene and terminator for herbicide tolerant soybean ACS-GM005-3. Yet CODEX is the international food safety guideline, and it includes significant specific criteria and risk assessment descriptions.

The Convention on Biological Diversity is an international agreement related to safe handling, transportation, and use of GE organisms if the shipment includes living modified organisms. It was adopted in 2000 and took effect in 2003 after 170 countries signed it. But the United States did not sign it. The USA is an observer but cannot vote on actions. Many countries in Africa including Tanzania, Uganda, Rwanda are using the Protocol to prohibit the import of any GMO (rather than LMO), so scientists are not allowed to bring in de-vitalized (non-LMO) GM material to test for detection limits and nutritional, or allergenic or toxic properties. Those rules are also practiced in Kenya and Nigeria even though both countries are accepting some GMOs as I found out in 2023 when three of us from the University of Nebraska–Lincoln went to Kenya on a follow-up to a USDA FAS grant for international academic education. Each country has different regulatory groups working on various aspects of agriculture, importation, plant health, human and animal health. We arranged for a representative from DSM in South Africa to bring lateral flow detection tests (protein-specific antibodies for detection of GM proteins) in to demonstrate to regulators and academic scientists that methods exist to help control LMO/GMO shipments. We had to get the National Biosafety Authority to bring some samples, or we would have had to register that materials we wanted to bring in, which were ground up corn grain, impossible to grow a plant from. It turned out that we had imperfect communications between DSM and the National Biosafety Authority and samples of the correct GM intended for the lateral flow strips were not available. In addition to demonstration detection methods, it would be

useful to bring in devitalized materials for nutritional testing, or even as test samples for PCR testing of a new GMO.

CODEX and Cartagena Compatibility

South Africa is a signatory party to CODEX, and they follow the risk assessment process outlined in CODEX (2003).² They also follow the Cartagena Protocol. It can be done. South Africa has approved 72 GMO events including some of canola, cotton, maize, rice, and soybeans.

Many other countries use the CODEX Alimentarius guideline for food safety, the OECD guidelines for feed safety and they follow the Cartagena Protocol for environmental safety. However, the Cartagena Protocol does add an extra burden on developers. And having both can lead to internal conflicts and delays in approvals. Most commercial crops or animals are unlikely to add an environmental risk like the Kudzu vine, or Short Ragweed pollen issues.

Issues of potential diseases such as bringing in new plant pests or plant and animal viruses do pose a significant risk between countries. Most countries including the United States and Kenya do have management systems to evaluate imports for plant and animal diseases and quarantine them if a problem is evident. They are not foolproof. Safety systems in all countries are imperfect. How did we get COVID-19 as a global pandemic? If biotechnologists were making recombinant viruses or microbes with the intent to release them, considerable safety evaluations are appropriate. But neither CODEX nor the Cartagena Protocol would be likely to detect and prevent those risks.

Scientific Advances That Enabled GMOs

Science students and academics today stand on the shoulders of scientific giants to enable our current advances. Understanding evolution was made possible by observations and writings of Darwin and Wallace and many before them. Plant breeding and genetics were advanced by the principles of Mendel and others skilled in care of plants and breeding. Barbara McClintock observed chromosome behavior in mitosis and meiosis and because of the genetics of maize

was able to predict and describe transposons that lead the way to understanding complex genetic changes important in evolution. Watson and Crick used information from Rosalind Franklin's X-ray crystallography work to complete a picture of the double helix. Many people worked on sequencing and understanding the human genome that is still not complete and contrary to Watson's prediction in 1992 that we would soon know and understand many genetically inherited diseases, we are still advancing knowledge of many diseases 30 years later. Certainly, DNA and RNA sequencing and protein mass spectrometry have advanced our understanding of life and heritability. We have learned to make recombinant constructs that allow incorporating traits from unrelated plants and animals that are useful in fighting plant disease and animal diseases, often improvements that seem mundane, such as drought tolerance with a cold-shock gene. And now as we learn more, we can use gene editing with CRISPR/Cas9 and other variations to more precisely alter the genetics of many species with or without the addition of foreign DNA. All advances take time, effort, and money to make sustainable changes to our productivity. We hope to make specific changes that benefit humans with little risk to ourselves or the environment. In the end, we are left with imperfect hazard identification and risk assessments, but we are far better at this than the observational trials that uncovered causes and risks of cholera, bacterial diseases, polio and the Irish potato famine. Yet, we have to thank plant breeders, farmers and others with good observational skills for much of our ability to exist as a species. We cannot exist as a species without some risks. We can minimize many of them. But we cannot wait for perfect safety to produce enough food for the growing population expected by 2050.

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