



Food safety risks and consumer health

Bruce M. Chassy

Dept. Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, 1101 West Peabody, Urbana, IL 61801, USA

The major food safety risks are not eating a healthy diet, and failure to avoid foodborne illness. Over one billion people in the world suffer from food insecurity and malnutrition. Nutritionally enhanced transgenic crops such as Golden Rice are one potential strategy for reducing malnutrition in the world. Transgenic crops are subjected to a rigorous pre-market safety assessment. The safety of novel proteins and other products is established, and through compositional analysis and animal studies, the safety of any observed changes is evaluated. These studies provide evidence that the new product is as safe as, or safer than, comparable varieties. It must be asked, however, if this rigorous analysis is necessary, because unregulated crops produced by other breeding methods also undergo genetic changes and contain unintended effects. Golden Rice poses infinitesimally small, if any, risk to consumers whilst it has the potential to spare millions of lives each year. However, because it is a transgenic crop, it cannot be deployed without years of expensive pre-market safety review. Paradoxically, if Golden Rice had been produced by less precise conventional methods of breeding, it would already be in the hands of poor farmers. It is concluded that the hyper-precautionary regulatory process applied to transgenic crops works to the extreme disadvantage of the hungry and the poor.

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E-mail address: bchassy@uiuc.edu.

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Introduction

The need for an adequate and safe supply of food has been a driving force for innovation in agriculture and the food industry [1]. In developed countries, consumers have come to expect that supermarkets will be amply stocked with safe and nutritious food. Affluent consumers hear food safety scares through the media almost daily and are bombarded with messages that question if government and industry are taking all possible measures to ensure food safety. Food safety regulatory agencies such as FDA in the US and EFSA in the EU, and similar agencies in other countries, have been charged with ensuring the safety of the food supply [2].

The situation is far different in developing countries where a significant portion of the population can suffer from under-nutrition or malnutrition, and micronutrient deficiencies are common ([3,4]; see also: <http://www.gainhealth.org/about-malnutrition/nutrition-facts>). Consumers in developing countries may be more concerned with obtaining adequate food supplies and ensuring food security than they are with food safety, although – paradoxically – their food is frequently contaminated with biological and chemical agents that have adverse effects on health (see: <http://www.who.int/mediacentre/factsheets/fs237/en/> [5]).

The development of the modern molecular plant breeding methods that employ rDNA technology and DNA-mediated transformation provided breeders with a powerful tool for crop improvement. Over the past dozen years, transgenic crops that are resistant to insects, viruses and herbicides have increased yields and profitability of agriculture, and reduced the environmental impact of agriculture, in both developed and developing countries [6,7]. These crops have proven especially beneficial to more than 12 million small-holder farmers in developing countries [8]. Plant breeders have also used the technology to improve the nutritional value of crops designed to reduce malnutrition and improve health [9,10]. Progress towards the introduction of nutritionally enhanced crops has been slower than for crops with improved agronomic traits. To date, transgenic high lysine maize and oil-seeds with modified oil content are being planted; many nutritionally enhanced crops are undergoing development and testing ([9,10]; see also The Safety Assessment of Golden Rice (GR) below).

Transgenic crops are required to pass a pre-market safety review by food safety regulatory agencies before they can be distributed freely [2,11,12]. Paradoxically, crops produced by ‘conventional’ breeding technologies are not required to undergo pre-market testing. As will be discussed in this paper, from a purely scientific perspective, transgenic crops pose no new or different safety risks when compared to conventionally bred crops [13–15]. The reasons why nations chose to single out transgenic crops for regulation as novel foods are beyond the scope of the present paper [16]; however, one of the motivations for regulation are consumer concerns – inflamed by activist groups that oppose what they call

‘genetically modified’ or GM foods – that foods produced using transgenic technology might be unsafe.

This paper will briefly describe: (1) a scientific risk assessment of the most important food safety risks that confront consumers, (2) the process used for a food safety assessment of novel foods, (3) questions about the safety of GR and (4) the damaging consequences of over-regulation of transgenic crops. Throughout the text, differences between the conclusions of scientific risk assessors and consumer perceptions about food-related risks will be highlighted.

Diet and global health

Malnutrition results from under-consumption, over-consumption or consumption of food that provides an inappropriate distribution of nutrients. Malnutrition, poor diet choices and over-nutrition have, or will have, an adverse impact on more than one half of the world’s population over the course of each individual’s lifetime. This paper will focus briefly on malnutrition and the poor. Suffice it to say here that affluent consumers are more concerned with consuming the right nutrients and avoiding overindulgence than they are with food insecurity.

Food insecurity affects about 1 billion people across the globe (Fig. 1). It is estimated that at least 10 million children die each year from malnutrition, that 150 million children are underweight and that 178 million are stunted ([3,4]; <http://www.gainhealth.org/about-malnutrition/nutrition-facts>). Morbidity and mortality owing to under- and over-nutrition are but the tip of the iceberg of a global diet that is inadequate to meet the world’s health needs. Associated losses include failure to reach full mental and physical development by 100s of millions of children, loss of economic productivity by workers, reduction in national GDPs and a larger and ever-increasing global bill for medical care. Scarcity of food energy and micronutrients takes a staggering toll of the poor, particularly in underdeveloped countries ([3,4]; <http://www.gainhealth.org/about-malnutrition/nutrition-facts>).

Iron deficiency, iodine deficiency, zinc deficiency, folic acid deficiency and vitamin A deficiency (VAD) are amongst the leading micronutrient deficiencies; one or more of these effects almost half of the world’s population ([17], <http://www.gainhealth.org/about-malnutrition/nutrition-facts>). VAD causes 250,000–500,000 cases of child blindness each year; half of the blinded children will die within 12 months. In 1992, WHO estimated that between 1.5 and 2.3 million deaths per annum can be attributed to VAD ([18]; Fig. 2); however, the exact numbers of deaths caused by VAD are difficult to assess because diarrhoeal disease and/or infection are often the direct causes of death in malnourished individuals with weakened immune systems; VAD also often occurs simultaneously with protein, energy and other micronutrient deficiencies that confound an exact diagnosis [17]. International programmes

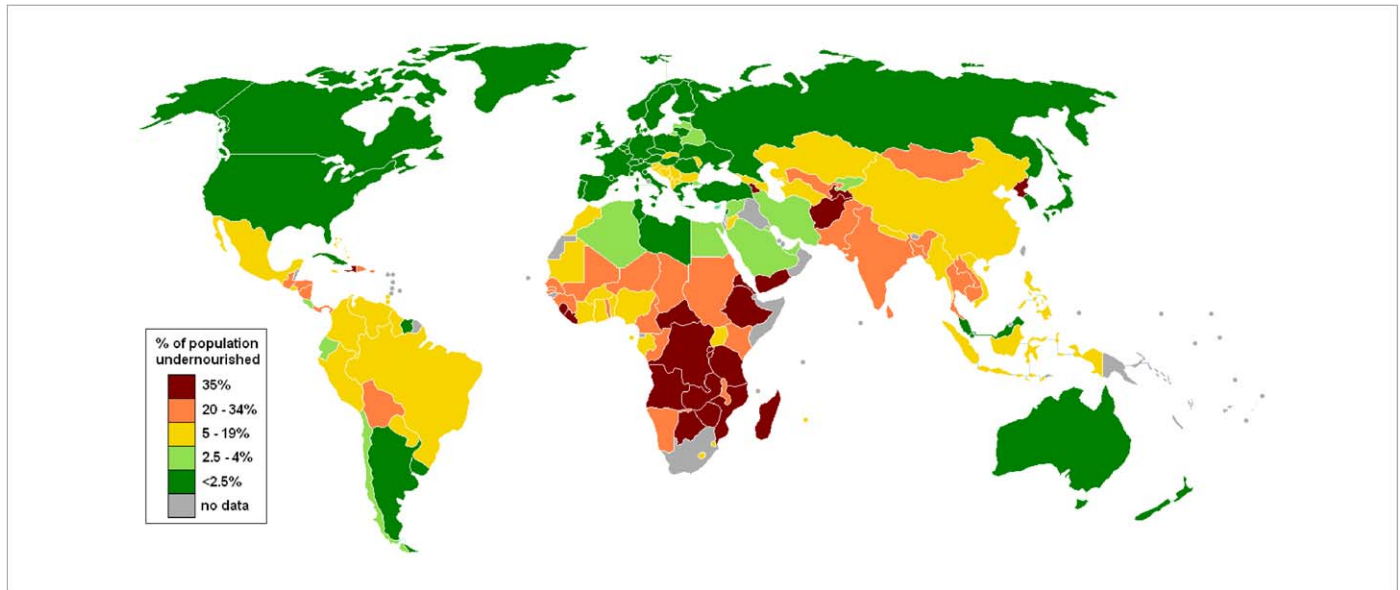


FIGURE 1

The percentage undernourishment of the world population by country (as reported by Lobezón in 2007 (http://en.wikipedia.org/wiki/File:Percentage_population_undernourished_world_map.PNG)).

designed to reduce VAD using modalities such as supplementation with capsules or injections have no doubt reduced VAD; however, these programmes are expensive, require recurrent treatment and do not reach the majority of the affected population. Because

approximately 70% of the VAD in the world is found in populations that consume rice as a major dietary staple, GR was developed as an adjunct or supplement to other VAD amelioration programmes ([9]; http://www.goldenrice.org/Content3-Why/why1_vad.html). GR is a transgenic plant variety for which a pre-market safety review will be required before it can be distributed to farmers in countries where VAD is prevalent (see The Safety Assessment of Golden Rice).

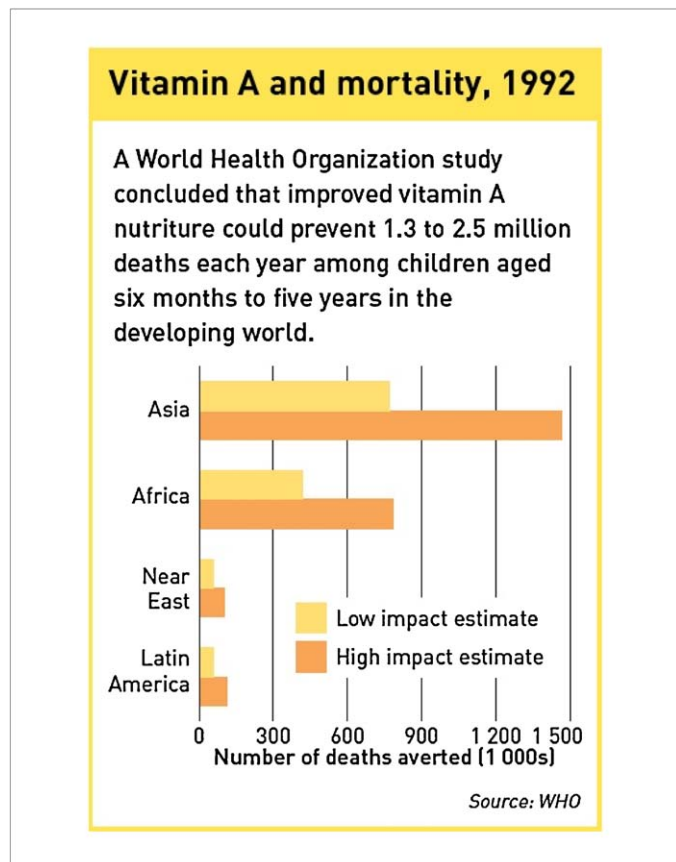


FIGURE 2

VAD mortality in 1992 [18].

Foodborne illness

Bacterial and viral pathogens that are present in consumed food and beverages can infect humans and cause foodborne illnesses. Food is also sometimes contaminated with preformed toxins produced by bacteria before food consumption. Ensuring that the risks of foodborne disease are minimised for the consumer is a major concern for food manufacturers, processors and retailers [19]. Achieving microbial food safety is problematic if proper hygiene and sanitation cannot be maintained. This is often the situation that confronts the very poor and, as a consequence, WHO estimates that 1.8 million people died in the world in 2005 from the effects of foodborne illness (<http://www.who.int/mediacentre/factsheets/fs237/en/>). WHO also notes that whilst most cases of foodborne disease are isolated and affect only one or a few individuals, widespread outbreaks that affect hundreds of thousands of people have been reported.

As noted previously, although affluent consumers in developed countries expect their food to be completely safe, the total elimination of viruses and bacterial pathogens is virtually impossible. Globally, billions of meals are consumed each day in an environment where potential pathogens are ubiquitous – not only are foods handled by humans, but also the ingredients themselves may be contaminated [19]. It has been estimated that foodborne diseases cause approximately 76 million illnesses, 325,000 hospitalisations and 5000 deaths in the United States each year [20].

Some affluent consumers have turned to organic foods in the belief that they are safer, more nutritious and better for the environment. It is ironic that organic foods may fall short on all the aspirations of consumers. There is no evidence that organic products are more nutritious [21], nor do they appear to be uniformly superior for the environment [22,23]. From a food safety standpoint, organic foods have been observed to have higher bacterial counts than their conventional counterparts and have been associated with foodborne disease outbreaks. The exclusive use of organic fertilisers such as composted manure in their cultivation may be responsible for the higher number of outbreaks and pathogens associated with organic products [21–23]. The objective here is not to attack organic foods *per se*, but simply emphasise the point that ensuring the best possible food safety depends on a science-based understanding of the food system rather than on value preferences and lifestyle choices such as consuming conventional versus organic foods.

Mycotoxins

Mycotoxins are toxic secondary metabolites that are produced by fungi and are found primarily in grains, tree nuts and groundnuts, but which also can be passed through animals into products such as milk [24]. The toxic components of poisonous mushrooms can also be considered mycotoxins because mushrooms are classified as fungi. About a dozen families of mycotoxins cause diseases as varied as liver cancer, kidney cancer, oesophageal cancer, neural tube defects (NTDs), liver and kidney toxicity, gangrene, convulsions, CNS malfunctions and suppression of the immune system [5,24]. Consumption of mycotoxin-contaminated feeds by production animals is estimated to cause billions of dollars in losses to farmers around the world through adverse effects on animal growth and reproduction.

Somewhat surprisingly, the impact of mycotoxins on human health is not well understood because it has not been the subject of extensive investigation. Some countries set safe upper limits for various mycotoxins in foods, raw materials and ingredients, whilst others have no system of assay or control, in spite of the fact that mycotoxins are amongst the most toxic and carcinogenic chemicals known to science [5,24]. For example, hundreds of Kenyans are reported to have died of acute aflatoxin poisoning in 2004 [25]. It has recently been suggested that the adverse health effects of two classes of mycotoxins, fumonisins and aflatoxins, have been seriously underestimated, particularly in many developing countries where products that are prone to mycotoxin contamination make up a large portion of the diet [5]. Often these same countries have no means to test or control for the presence of lethal mycotoxins. The major impacts of these mycotoxins are liver and oesophageal cancers, hepatitis, NTDs and productivity losses in animal agriculture. Fumonisin contamination is typically a pre-harvest event, whilst poor storage conditions often lead to post-harvest aflatoxin contamination. Strategies for prevention and remediation exist but are not widely employed prompting Wild and Gong [5] to conclude:

“Notwithstanding the need for a better evidence-base on mycotoxins and human health, supported by better biomarkers of exposure and effect in epidemiological studies, the existing data are sufficient to prioritize exposure

reduction in vulnerable populations. For both toxins there are a number of practical primary and secondary prevention strategies which could be beneficial if the political will and financial investment can be applied to what remains a largely and rather shamefully ignored global health issue.”

Biotechnology provides an excellent strategy for the prevention of fumonisin contamination of maize [5,26]. There is clear evidence from the SW US, Guatemala and South Africa that women who eat a diet that is high in fumonisin-contaminated maize content give birth to a higher percentage of NTD-birth defect babies than otherwise matched populations that eat less contaminated maize products. It is known that fumonisin interferes with folic acid uptake by cells and thus mimics folic acid deficiency that is known to give rise to NTDs. It has also been demonstrated that the amount of insect damage to maize kernels has a positive correlation with levels of fumonisin and that Bt-maize (insect-protected transgenic maize) which suffers far less insect damage typically has markedly lower levels of fumonisins [5,26]. The planting of transgenic Bt-maize is therefore an efficacious means to lower exposure to fumonisins and thereby reduce the incidence of birth defects as well as oesophageal and kidney cancers.

As noted previously, affluent consumers in developed countries are enamoured with organic foods that they perceive to be safer than food prepared with ingredients isolated from conventional and transgenic crops. A consequence of the requirement in organic agriculture that no synthetic chemicals be used in cultivation is that control of fungi on organic crops is challenging for the organic farmer and organic crops can at times contain higher levels of mycotoxins than their conventional counterparts [23]. In 2003 the UK Food Standards Agency randomly sampled 30 corn meal (maize meal) products found on the shelves of UK supermarkets [27] and found that 6 out of 6 samples of organic corn meal contained fumonisin levels more than tenfold higher than the maximum safe level set by the FSA (Table 1). By contrast, 20 of 24 samples of corn meal prepared from conventionally cultivated maize were found to have fumonisin levels below the recommended safe maximum; 4 samples of conventional corn meal exceeded the recommended safe level (Table 1). Other studies have shown that Bt-maize protected against stem-boring insects

TABLE 1
Total Fumonisin content of cornmeal brands from UK supermarkets [27]

A. Low fumonisin			
Type	# Below ^a 500 µg/kg	Mean (µg/kg)	Range (µg/kg)
Conventional	20	130	10–330
Organic	0	–	–
B. High fumonisin			
Type	# Above 500 µg/kg	Mean (µg/kg)	Range (µg/kg)
Conventional	4	3127	1798–4737
Organic	6	8353	3800–16,430

^a Recommended upper limit of fumonisins is 500 µg/kg.

generally contains far lower levels of fumonisins than conventional maize [5,26]. Thus, whilst many consumers perceive that there may be food safety risks associated with 'GM' maize, there is clear evidence that switching to transgenic maize could lower the incidence of certain cancers and birth defects.

Natural toxicants

Plants produce a variety of toxic molecules as part of their defences against predators and competitors [28]. During the process of crop domestication, the concentration of such toxicants is often reduced. Food processing and preparation methods, as well as consumption patterns, help control any potential adverse effects to humans and animals associated with plant-derived foods. Commonly eaten foods can, however, be toxic to humans [29,30]. Most consumers would be surprised to know that deaths resulting from ingestion of green tomatoes or potatoes containing high levels of glycoalkaloids (e.g. solanine, tomatine and chaconine) have been documented [30–33].

Many consumers buy organic foods because they are concerned about the presence of trace amounts of synthetic pesticide residues in their food. A careful analysis of pesticide intake in 1990 concluded that 99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves [32]. Evidence also indicated that natural pesticides were as likely as synthetic pesticides to be carcinogenic, and that the risk from exposure to dietary synthetic pesticides is insignificant, whilst so-called 'natural pesticides' that are used in organic agriculture, such as pyrethrin, are as likely to be carcinogens as synthetic pesticides [33,34]. Consumers are largely unaware that pesticides are even used in organic agriculture believing them to be 'pesticide free'; they are also unaware that plants manufacture their own *natural* pesticides. Although synthetic pesticide residues pose insignificant risks to consumers, the risks posed by *natural* toxicants in foods remain largely unstudied. Doll and Peto [35], estimated that approximately 35% of cancer deaths are attributable to variation in diet. It may be that over-nutrition and its consequences are the cause of most of these deaths; however, a role for endogenous *naturally occurring carcinogens* on the incidence of cancer cannot be excluded.

In spite of the fact that the safety of approved food ingredients and food additives must be established before their use in foods, and it must be demonstrated that they will pose no risk when used as intended, in recent years consumers have expressed fears that chemicals added to foods will do harm unless they are *natural* chemicals. This completely misses the underlying scientific understanding that any chemical can be toxic and it is only the dose and exposure that determine if a chemical will do harm in a specific situation [36]. To learn that a compound is *natural* does not in any way inform a toxicological food safety assessment. Somewhat paradoxically, the public eagerly consume large quantities of antioxidants and other chemicals whose safety and efficacy have not been tested, in the belief that such compounds will prevent ageing and ensure good health.

There is ample reason to believe that small amounts of some chemicals that are toxic at high doses may in fact stimulate health when consumed in sub-toxic quantities through a phenomenon known as 'hormesis'; a compound that exerts a hormetic effect may have a positive beneficial effect at low levels of intake, whilst at high levels of intake it produces adverse effects and harm [37]. It

may be that low levels of exposure to various potential toxicants actually stimulate or induce our natural immunological defences and detoxification systems, rendering the body more resistant to subsequent chemical threats. It cannot simply be assumed that because a chemical is toxic or causes cancer at high doses, that it will not be innocuous, or even beneficial, at lower doses. Toxicologists emphasise that the dose makes the poison.

One example of an unexpected outcome of hormesis was observed by researchers studying the impact of antioxidants on ageing in *Caenorhabditis elegans*, a small worm used as a model system in biology [38]. In *C. elegans*, as in many other species in which the phenomenon has been studied, mild to moderate caloric diet restriction increases life span. Paradoxically, it also produces a syndrome called 'oxidative stress' that has been proposed as one of the factors that leads to ageing. To evaluate the impact of this oxidative stress on the organism, the researchers treated one group with antioxidants that were known to eliminate oxidative stress. The result observed was that the prolongation of life produced by caloric deprivation was eliminated by antioxidants. The researchers speculated that the oxidative stress had a hormetic effect that allowed the organisms to fend off ageing reactions and that by cancelling out the oxidative stress, antioxidants shortened rather than lengthened life. It is noteworthy in this regard that millions of consumers spend billions of US\$ annually on antioxidants that could be shortening rather than extending life spans. The important point here is that sound diet choices are based on sound science, not wishful hopes, and scientific understanding of the complexities of slowing the ageing process has not been unravelled.

A food safety perspective on novel foods

As had been previously noted, transgenic crops are subjected to rigorous pre-market safety assessment, in spite of the fact that they can be less genetically modified than crops produced by other modalities of breeding. They pose no new or different risks to humans or animals. Precautionary regulation was triggered because these crops were considered to be novel foods – foods that humans had not previously consumed. This definition is itself debatable because it is fair to ask if an organism into which one or two genes have been added to 20 or 30 thousand genes in the plant genome makes the plant a novel food. From a purely scientific perspective it is simply a crop variety that has one or two novel traits; crop varieties often differ by two or more genes. Most of us expect, however, that some degree of care and safety consideration should be taken before one consumes a food that one has never seen before and which is not commonly eaten. We will return to the issue of the safety of novel traits in the next section and will here explore the history of novel foods.

The great majority of the plant foods that we consume today did not exist before the development of agriculture approximately 10,000 years ago [1]. In 1859, Darwin [39] described the process of domestication of wild plants and their gradual evolution through a process of human-directed selection into crop plants. Domestication is brought about through selection of several genetic modifications that, for example, increase yield, reduce toxic molecules and improve harvest qualities. At the end of the process, the domesticated plant has often lost all resemblance to its wild progenitor and can no longer grow in the wild, but depends on cultivation by humans for survival [15]. Different crops were

TABLE 2

Origins of some common crops ([1]; see also <http://www.hort.purdue.edu/newcrop/history/lecture05/lec05.html>)

Crop	Origin
Avacado	Central and South America
Beans	Mesoamerica
Cacao	Aztec (xoco-latl)
Corn (maize)	Mesoamerica
Cotton	South America
Gourds	Americas
Papaya	Tropical America
Peanuts	South America
Peppers	Mexico-Mesoamerica
Pineapples	South America
Potatoes	Andes Mountains
Pumpkins	Tropical America
Squash	South America
Strawberries	Americas
Sunflowers	Central and North American
Tomatoes	Mesoamerican

developed in various locales and became part of the local or regional cuisines.

Over thousands of years, some crops such as wheat were widely disseminated across the Eurasian landmass [1]; however, many crops remained restricted in distribution until the era of European exploration and colonisation and the establishment of global trade routes. For example, varieties of crops that were restricted to the Americas were not found elsewhere in the world until Spanish Conquistadores brought them to Spain upon their return from the New World (Table 2). In particular, maize (the world's number one grain crop), tomatoes (a leading vegetable crop) and potatoes

TABLE 3

Incomplete list of toxic and allergenic plants that would not pass the current safety assessment applied to GM crops

Crop	Harmful substance
Celery	Psoralens (furanocourmarins)
Potato, tomato	Glycoalkaloids
Cassava	Cyanogenic alkaloids
Rubarb, spinach	Oxalic acid
Soy, wheat, milk, eggs, mollusks, crustaceans, fish, sesame, nuts, peanuts, kiwi	Food allergy

(the world's 4th most important staple crop) were unknown throughout most of the world until sometime after the 16th century. All of the crops listed in Table 2, and many others from other parts of the world, were introduced as wholly novel foods to humans the world over during the past 300–400 years ([40]; Fig. 3). They appear to have been very readily adopted, and the globalisation process appears to have occurred largely with without adverse health effect.

It is noteworthy that many of the crops that were disseminated around the globe over the past few hundred years contain toxic components and are potentially deadly if not prepared and consumed properly. Cassava, for example, moved from the Americas to Africa and Asia where it was widely adopted in spite of the fact that it contains highly poisonous cyanogenic compounds that can kill if not properly removed through tedious and complex preparation. Potatoes and tomatoes, as noted previously [30,31], contain toxic glycoalkaloids (tomatine, chaconine and solanine) as do all the *Solenaceae* of the Nightshade family. There is in fact a long list of potentially toxic plants that have crossed international frontiers and cultural barriers in spite of apparent hazards (Table 3). Many of these crops would not be approved for distribution if they were subjected to the standards that are applied to GM

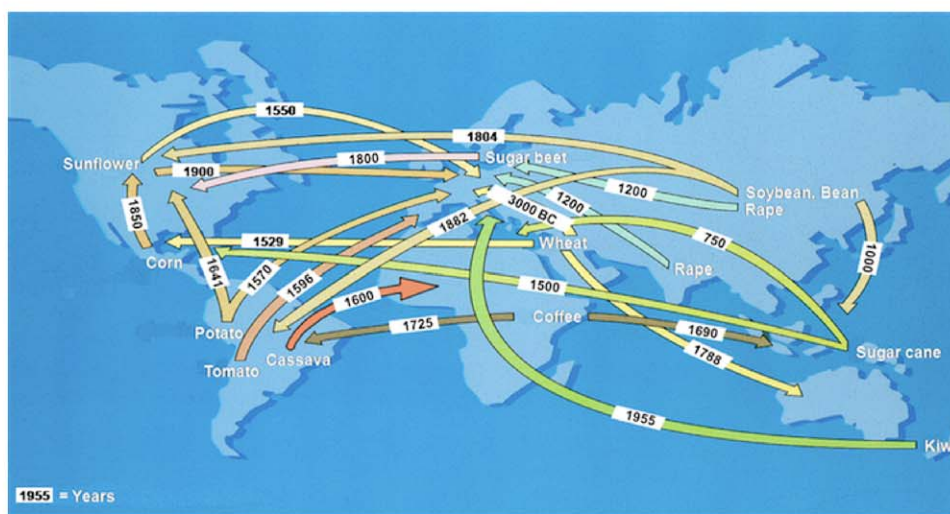


FIGURE 3

Map of history of movement of crops around the globe [40].

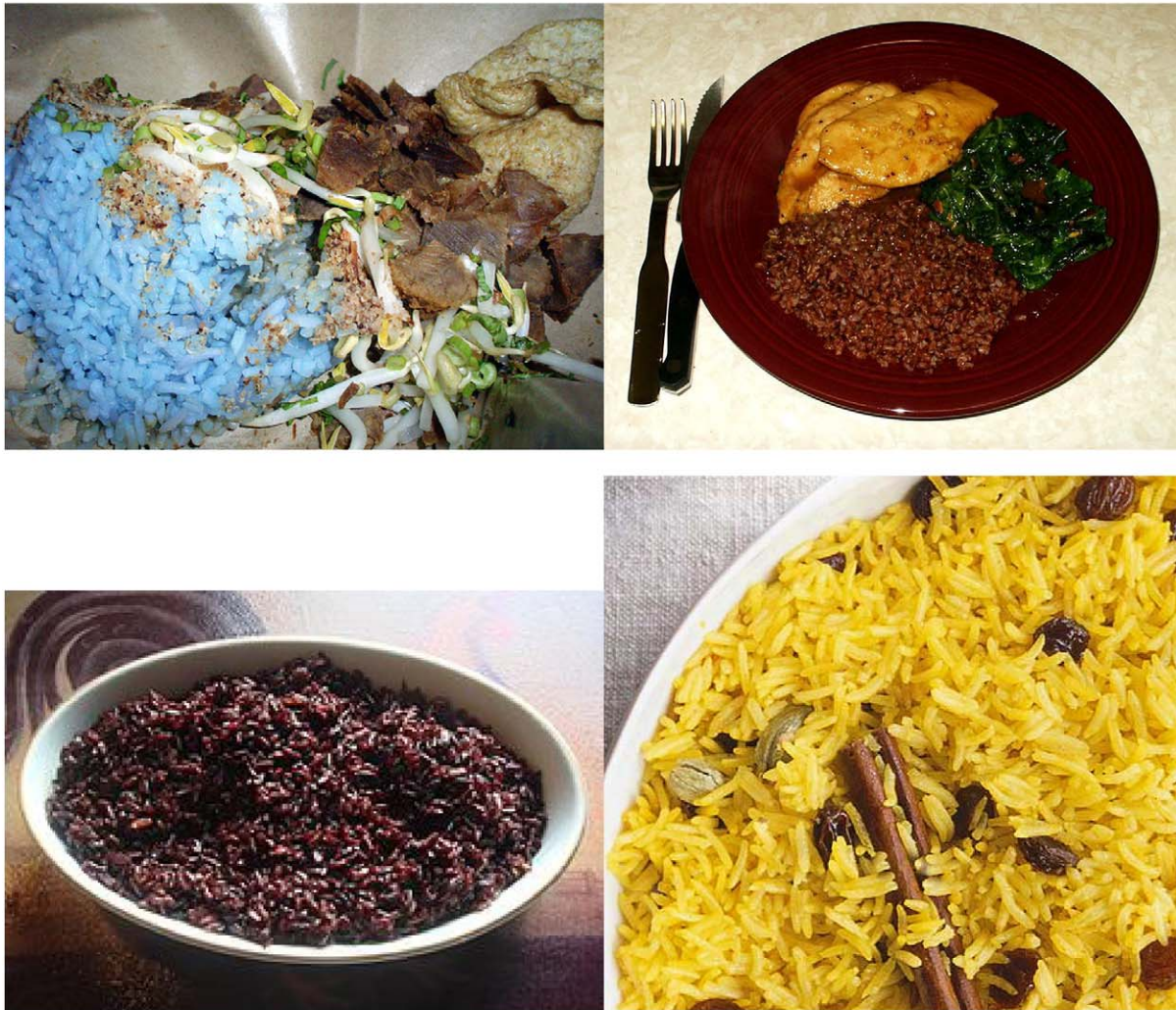


FIGURE 4

Coloured rices. Starting in the upper left-hand corner and moving clockwise the rice dishes are: Malaysian Blue Rice (<http://www.haveyoueaten.net/2007/09/28/nasi-kerabu/>); Bhutanese Red Rice (Glane23, Flickr; http://upload.wikimedia.org/wikipedia/commons/4/40/Bhutanese_red_rice_with_chicken_and_spinach.jpg); Saffron Rice (<http://www.saffronspices.co.uk/wp-content/uploads/2009/02/saffron-rice.jpg>); Black Rice (<http://www.thenibble.com/reviews/MAIN/rice/images/black-rice-250.jpg>, ElinorD).

crops today around the world. If international treaties such as the Cartagena Protocol on Biosafety, that seeks to restrict movement of LMOs (living modified organisms) across borders, had been in place during the era of crop globalisation, the historical trans-boundary movement of crops depicted in Fig. 4 would not have occurred.

The safety of transgenic crops

It is not an easy matter to ensure that a truly novel food is safe, because foods are composed of hundreds or even thousands of distinct metabolites, some of which may be allergenic or poisonous. The safety assessment process applied to the mycoprotein product Quorn provides a good example of the challenges of assessing the safety of a whole food. Quorn is a single-cell protein product that can be formed into cheese, meat or poultry-like foods [41]. Researchers performed extensive compositional studies, fed the material to animals, rubbed it on their epidermis, injected it

under their epidermis, fed it human volunteers and at the end of the day called for approval of the product even though there was no clear test to show the product was safe; what could be demonstrated was that its composition was similar to other high quality protein foods and that it was apparently innocuous to living subjects when consumed by them. Approval was granted in spite of the fact that about 1 in 100,000 people, who consumes the product has an adverse reaction.

The safety assessment process applied to transgenic crops, foods and feeds should be much more straightforward than that described for Quorn because only one, or at most a few genes, are inserted and the changes that are introduced are small, well-defined and usually predictable [2,9,42,43]. Transgenic crops are not wholly novel foods as was the case in the case with Quorn. In the case of transgenic crops, the crop is essentially unchanged, except for the intended additions. When a gene is inserted into a plant, three questions emerge:

1. Is the inserted DNA safe to consume?
2. Is the product(s) of the gene safe to consume?
3. Are the intended, and any unintended changes, safe to consume?

Several recent reviews have discussed the food safety assessment process that is designed to evaluate the above questions [2,9,42,43]. Although regulators set high standards for evidence and require that uncertainties be resolved before approval of a new transgenic crop, several key issues discussed in the recent reviews [2,9,42,43] continue to concern consumers and will be discussed briefly below.

Substantial equivalence

The comparative safety assessment paradigm that is used by regulators to guide the safety assessment process is called the substantial equivalence paradigm. There have been claims that GM crops are never identical to their conventional counterparts, so it is incorrect to call them substantially equivalent and that, because they are not identical, they are not safe. It is important to recognise that developers and regulators do not claim that new transgenic varieties are identical to their conventional counterparts because, as a result of any breeding process, no two varieties of any crop have the same composition [43]. More importantly, what the substantial equivalence paradigm actually asserts is that components that are identical between two crop varieties pose the same risk, and that any differences in risk between two varieties are restricted to components that are present in different amounts. Substantial equivalence does not require that two varieties be identical, indeed, if two varieties of any crop are identical they are not distinct varieties. Safety assessors use the substantial equivalence (or comparative assessment) paradigm as a guide to differences whose safety must be evaluated.

Safety of DNA

There have been several claims that transgenic DNA could become incorporated into human or bacterial cells and give rise to cancer or promote the spread of antibiotic resistance [9,44,45]. Research has demonstrated that transgenic DNA is no more or less likely to be transmitted than other DNA and it is important to note in this regard that humans consume >100 mg DNA per day which is digested and metabolised without ill effect. Careful studies have also demonstrated that antibiotic resistance genes are ubiquitous in the environment and transgenic crops have not added to the spread of antibiotic resistance. The spread of antibiotic resistance is most probably the result of poor stewardship in the use of antibiotics by humans [45].

Safety of transgenic proteins

The vast majority of dietary plant proteins are digested and absorbed without any adverse effect, although a very few proteins can be toxic or have anti-nutrient activity, for example, trypsin inhibitors in soybeans [46]. Similarly, very few proteins are food allergens; most known food allergens affect less than 0.1% of the population [47]. The sequences of virtually all known toxic or allergenic proteins have been determined and using that information it is possible to test if a newly introduced protein resembles in any way proteins that are known to be toxic or allergenic. If a

protein resembles an allergen or toxin in any way, further research is discontinued. Tests are also done to determine if a protein is quickly digested, which adds further assurance that the protein is safe to consume [47]. It is important to remember that a transgenic protein is no more likely to be an allergen or toxin than any other, and perhaps less likely since careful pre-market screening is required of transgenic crops but not crops produced by other less precise and more genome disruptive breeding technologies [46,47].

Unintended effects

The critics of GM crops continue to assert that inserting DNA into a plant genome could cause unintended effects that might be harmful. A large body of evidence points to a very different conclusion: transgenic insertion can produce fewer unintended effects than other forms of breeding [13–15]. Unintended effects occur in all forms of breeding; however, compositional and phenotypic analyses, as well as extensive backcrossing, are used by breeders to cull out unintended effects.

The Safety Assessment of Golden Rice

Although vitamin A is retinol, many humans acquire vitamin A by synthesising it from β -carotene derived from plant sources such as carrots and orange-fleshed sweet potatoes in which it is abundant. Unfortunately for the billions of people who depend on rice as the major portion of their diet, white or polished rice contains no β -carotene [9,48]. GR was constructed by inserting a cassette of DNA containing genes for phytoene synthase (ex daffodil; *Narcissus pseudonarcissus*) and carotene desaturase (ex *Erwinia herbicola*) into rice (*Oryza sativa*) to allow the plant to synthesise β -carotene from its precursor, geranyl-geranyl-diphosphate [48]. A second version of Golden Rice (GR2) was produced by the use of a phytoene synthase gene from maize (*Zea mays*) in lieu of the gene from daffodil used in GR. GR contains about 1.6 μ g β -carotene/g rice and GR2 contains about 10–40 μ g β -carotene/g rice [49]. The β -carotene content of the rice makes GR a light yellow or golden colour whereas GR2 has more intense amber golden colour. A case study of the key elements for the safety assessment of GR2 has been published [9]; the safety assessment of transgenic rice varieties in general has also been reviewed [42]. In the following paragraphs key points in the safety assessment and adoption of GR will be discussed.

DNA safety

As noted previously, DNA is safe to consume. To address negative perceptions about the safety of antibiotic resistance genes used as markers in transgenic plants, GR2 was constructed using the phospho-mannose-isomerase (PMI) marker system that allows the simple sugar mannose to be used to select transformants. The system has been used in other transgenic crops and has been approved by regulators.

Protein safety

Allergy to rice is uncommon and rice contains no major anti-nutrients or toxins. The sequences of the proteins produced by rice plants containing the GR and GR2 constructions have been compared to all known toxins, anti-nutrients, lectins and food allergens with no similarities detected. The maize phytoene synthase

protein that was incorporated into GR2 is commonly consumed by humans and animals. The PMI marker system has been consumed in other approved transgenic crops and the enzyme itself is ubiquitous in nature, including in bacteria found in the human gut, and has no similarity to any known allergen or toxin; the protein is also digestible. The bacterial carotene desaturase protein is the only protein that will be unique to the human diet, and for this reason, extensive safety analysis of this protein (and perhaps the others mentioned above) will be required. Large quantities of the protein will be required for animal toxicity studies; small amounts will be used for digestibility studies. Other studies will be required to determine the quantity of each of these proteins present in the rice, and that the proteins are identical to the corresponding protein found in the donor of the gene that encodes them. It is worth noting that these rigorous protein safety tests will be required by regulators even though the quantities of proteins present will probably be far lower than would be required for most known toxins to exert a biological effect. That is to say, few potent toxins would have an adverse effect in the quantities these proteins are present in GR. Moreover, because rice is cooked at high temperature for long time periods, the proteins will be thoroughly inactivated and denatured and will thus likely pose no threat to humans and animals. It is worth repeating that proteins with but rare exception are safe to consume. It is difficult to understand the need for extensive protein safety testing on proteins that are present in infinitesimal quantities.

Composition analysis

The composition of transgenic crops is routinely evaluated as part of the process of establishing that there have been no losses in nutritional value and that no unintended changes have occurred. Because GR and GR2 varieties have been crossed with many different varieties that farmers grow in different growing regions in Asia, there will be many distinct compositional profiles collected for GR- or GR2-derived varieties. Particular attention will be paid to the pool of compounds associated with carotenoid biosynthesis and the carotenoids because this is the pool of metabolites targeted by the genetic engineers and most likely to have been affected. Composition testing is not required for rice varieties produced by other modalities of breeding. Additionally, rice is a very poor source of almost all required nutrients; rice mainly supplies carbohydrates for energy and limited quantities of proteins; the micronutrient content of rice is virtually nil. Composition testing is expensive and time-consuming and its value has been questioned [43]. Although it certainly is clear why the developers would need to know the concentration of β -carotene in each variety, because only a few micrograms of β -carotene per gram of rice are being added to the rice, it is far less clear why composition testing is even necessary.

Does GR contain enough β -carotene?

Critics of GR have claimed that GR would not provide the RDA of vitamin A. A careful analysis of this claim demonstrated that GR could indeed make an important contribution to vitamin A intake, although it might not provide 100% of the RDA [9,50]. Zimmerman and Qaim [50] calculated that GR could supply between 11 and 86% of the RDA. It should be noted that GR was intended as a supplement and that 100% of an RDA is not necessary to amelio-

rate VAD; intake of 25% of the RDA will prevent blindness and death. In addition, most users of GR will have some other sources of vitamin A in their diets. The key issue in debate over the effectiveness of GR centres around assumptions about the bioavailability of GR, with critics arguing that only one molecule of retinol would be produced from 25 molecules of β -carotene (a 1:25 ratio) and researchers countering that 1:6 or 1:12 would be a more likely scenario. The issue was recently resolved when it was reported that the conversion ratio in human subjects was close to 1:4 [51]. It is now clear that GR can make a significant contribution to vitamin A intake. GR2 is capable of providing an RDA of vitamin A in a single bowl of rice [9]. Any continuing claims to the contrary are not rooted in science or evidence.

Is the β -carotene in GR toxic?

Critics have claimed that adding β -carotene to rice may give rise to toxic degradation products and they point out that retinoids can exert toxic effects – which is correct. Their logic is, however, flawed. Carotenoids are not retinoids and they are not converted to toxic levels of retinoids *in vivo* at levels of exposure that occur in foods [52–54]. The conversion of β -carotene to retinol is a highly regulated and compartmentalised process that ensures that excesses of potentially toxic retinoids will not be generated. This controlled biological regulation might have in part evolved to cope with the fact many foods we eat contain β -carotene and other carotenoids and it would not be undesirable to convert them to toxic retinoids. It is noteworthy as well that GR contains less β -carotene than carrots, orange-fleshed sweet potatoes, papayas and several other commonly eaten plant foods. β -Carotene has also been consumed safely in even higher quantities by consumers for its anti-oxidant properties with no adverse reactions reported. It is thus uninformed or deliberately misleading to claim that the β -carotene in GR could be toxic. Parenthetically, arguing that GR has too little β -carotene to be of any nutritional value and also that it has so much β -carotene that it could be toxic is mutually inconsistent.

Will consumers accept Golden Rice?

Critics of transgenic crops rushed to claim that people will not accept any colour of rice but white. They based their claim on the well-known fact that people who consume polished white rice will often refuse to eat brown unpolished rice. This is an imperfect analogy because white and brown rice are very different foods with respect not only to appearance but also to flavour and texture. It should also be added that brown rice is also a better source of some nutrients than white rice. Brown rice does not keep well in tropical and semi-tropical climates where the great majority of rice is consumed. The real problem with the claim that people will not accept coloured rice is that the critics are also simply ignoring the fact that coloured rice foods are widely consumed around the world (Fig. 4). Yellow coloured or GR is the leading choice of discerning rice consumers. Saffron, annatto or achiote and tumeric are all extensively used in various countries to produce golden yellow rice dishes. Black rice was considered so desirable in ancient China that only the Emperor was allowed to consume it. The Bhutanese prepare red rice and blue rice is a specialty in Malaysia. Any objective reading of consumers' rice colour preferences suggests that rice colour *per se* is not necessarily a barrier to acceptance and can in fact be a desirable property. It should be noted that

research subjects that have tasted GR state that it tastes the same and has the same mouth feel as conventional rice. Perhaps the best way to test if GR is acceptable to consumers is to allow consumers the choice of deciding whether they want to plant it and/or grow it for themselves and their children.

The silent holocaust

As noted previously, VAD kills approximately 2 million people a year – most of them rice-eating children. If GR had been bred by conventional means, two or three years might have been required to propagate and distribute the seeds, and – assuming a reasonable adoption rate – perhaps the lives of a half a million or a million people a year might have been saved until now. GR was not, however, in any way conventional, it was a paradigm-shifting innovation. GR has instead been confronted with critics who have delivered a long list of ill-founded claims about safety and efficacy. GR has also confronted an intransigent regulatory system that requires millions of US\$ and many years to navigate for each new product. At ten years after the first development of GR, the world's VAD sufferers may still be two to five years away from receiving the seeds that could save their lives. Considering the minimal safety concerns associated with GR and the staggering annual toll of VAD, would it not have been a better choice to distribute the seeds just as would have been done if they were conventionally bred? The moral calculus is surprisingly simple: if GR had been distributed in 2002 or 2003, millions of lives might have been saved. Not to have disseminated the seeds of GR until now has allowed as many people to die silently as were killed in the holocaust.

Damage by distraction

Science-based risk assessment of the food system reveals that the adequacy and quality of the diet has more influence on morbidity and mortality, as well as quality of life, than any other food risk. Dietary choices affect all of us; however, the billion humans that do not have enough food, or a sufficient variety of nutritious foods to eat, are in extreme peril. Foodborne illness kills and sickens hundreds of millions of people each year, many of whom do not have access to sanitary supplies of food and water. Mycotoxins cause a significant portion of liver, kidney and oesophageal cancer in the world as well as birth defects, reproductive failure and a host of other ills most likely affecting hundreds of millions of consumers,

including affluent consumers living in industrialised countries. Plants can synthesise a wide variety of toxicants, anti-nutrients and allergens that can also adversely affect health. Although their impact on health has not been quantified, a considerable number of the chemicals that are naturally occurring plant secondary metabolites are carcinogens. These are the major food safety risks that need to be understood, avoided and/or managed.

By contrast, some consumers are more concerned about pesticide residues and chemicals in their food that pose little if any risk. Consumers perceive human-made chemicals to be inherently toxic and respond to each new claim that a chemical is a carcinogen, or – more recently – a pseudo-hormone or a hormone blocker. In some cases, it may be that the compound the public seeks to avoid might even be beneficial through a homeotic mechanism of action. Every year brings a new scare to television and newspapers. The consequence of these misperceptions about real risks is that consumers' buying choices are manipulated, as for example rushing to buy more costly organic food that is no more nutritious or safe than conventional foods, and which may arguably less safe in certain circumstances. Public pressure, as well as economic and political agendas, leads to attention being paid to relatively minor safety issues at the expense of investment of resources into control of safety issues that do real harm. Public concern about perceived risks is also often translated into stringent regulations that are not only costly, but which inhibit innovation and distract government, industry and consumer attention away from real risks. Ames and Gold [36] have coined the phrase 'damage by distraction' to describe this phenomenon.

Nowhere is 'damage by distraction' more apparent than in the way transgenic crops are regulated in the world today. In spite of scientific analysis that indicates that transgenic crops are as safe as, or safer than, crops produced by other breeding modalities, transgenic plants are treated as if they were toxic chemicals or nuclear waste. In the case of GR, negative perceptions and unscientifically stringent regulations have inhibited the introduction of a potentially lifesaving crop innovation. It is hard to imagine any food safety risk arising from transgenic rice that could rival the global impact of VAD. Precautionary fears have caused regulators and consumers to forego real benefits and not erase harms caused by current practices and products. One must ask in the final analysis if it is not *immoral* not to use a technology that can save lives.

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