Cell Press REVIEWS

Opinion

Risk-Only Assessment of Genetically Engineered Crops Is Risky

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The risks of not considering benefits in risk assessment are often overlooked. Risks are also often evaluated without consideration of the broader context. We discuss these two concepts in relation to genetically engineered (GE) crops. The health, environmental, and economic risks and benefits of GE crops are exemplified and presented in the context of modern agriculture. Misattribution of unique risks to GE crops are discussed. It is concluded that the scale of modern agriculture is its distinguishing characteristic and that the greater knowledge around GE crops allows for a more thorough characterization of risk. By considering the benefits and risks in the context of modern agriculture, society will be better served and benefits will be less likely to be forgone.

Highlights

GE crop risks should be considered in the context of modern agriculture.

The scale of modern agriculture is its primary distinguishing characteristic.

Greater knowledge favors better characterization of risks for GE crops.

Consideration of benefits in the risk assessment of GE crops benefits society.

Technological Advances

Risks and Benefits

Every new or improved technology, regardless of its particular field or application, can involve risk, potential risk, or perception of risk by stakeholders and/or end users. However, it is often overlooked that the rejection of technology also has risks in the form of missed opportunities for benefits. For example, a vaccine may cause allergic reactions in a small number of immunized individuals within a large population, but at the same time, a vaccine can greatly reduce the loss of life across that same population due to the immunity it provides to a serious disease [1,2]. Without considering the potential benefits of a new technology in its regulatory oversight and acceptance, society as a whole is ill served. An example where the benefits have been found to greatly outweigh the risks is the case of genetically engineered (GE) crops [3,4]. In jurisdictions where regulators consider risks and benefits of particular GE crops, such crops have been approved for cultivation and embraced by farmers in a way unprecedented for an agricultural technology [5] (Box 1). By contrast, where regulation focuses primarily on risk, without significantly weighing the context of the existing agricultural systems and the benefits GE crops bring relative to existing technology, farmers (and society) have been largely excluded from the environmental, health, and economic benefits of this technology [6–8]. Furthermore, the high cost of developing GE crops to meet risk-disproportionate regulatory requirements in countries that import significant volumes of food and feed crops has generally restricted the development of this technology to large multinational corporations aimed at wide-acre solutions for farmers in developed countries [9,10]. Here, we discuss the context of modern agriculture and qualitatively compare risk/benefit analyses versus risk-only analysis, highlighting the risk of rejecting GE crops in the latter framework.

Agricultural Context

Scale Defines Modern Agriculture

Although many attributes have been asserted to define modern agriculture, probably the most notable is its scale. Total farmed land area has increased in response to the growing world population [12]. This is particularly of importance today and in the near future since it has been

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Box 1. Benefits Accrue for Latin America

Brazil and Argentina, ranked second and third, respectively, in GE crop acreages, represent Latin American countries where regulatory systems have addressed risks in light of the benefits of GE crops and implemented this balanced approach within GE regulatory oversight. Since the first Brazilian GE crop was released in 1998, adoption has grown to greater than 88% for maize, 96% for soybean, and 78% for cotton crops in Brazil [5]. Being one of the six 'founder GE crop countries', Argentina introduced the first GE soybean and cotton in 1996. Partly attributed to its timely regulatory approvals, the GE adoption rate in Argentina in 2016 was 97% for maize, nearly 100% for soybean, and 95% for cotton. Adoption of GE crops in Brazil and Argentina has allowed for higher average farm income (cumulative economic benefit of US$24.8 billion for Brazil and US$21.1 billion for Argentina) realized largely through reduced selective herbicide costs and higher yield [5]. Another significant benefit for farmers in this region is enablement of a second crop per year due to the adoption of environmentally beneficial conservation tillage (facilitated by herbicide-tolerant GE crops). Similar farm income benefits have also been observed in other Latin American countries where GE crops are grown, including Bolivia, Colombia, Paraguay, and Uruguay [11]. Also noteworthy is the development of traits specifically targeting local Latin American pests due to functional regulations for GE cultivation. Furthermore, locally developed and cultivated GE common bean and GE eucalyptus trees are milestone achievements in Brazil [5]. More recently, in 2017, regulatory approval and commercialization of the locally developed pest-resistant GE sugarcane in Brazil may help to preserve the Brazilian sugar industry currently threatened by insect pests such as the sugarcane borer (http://www.isaaa.org/kc/cropbiotechupdate/article/default.asp?ID=16248).

estimated that the global population will increase to nearly ten billion people by 2050 [13]. Accordingly, this population growth is expected to require an increase in overall food production by 70% [14]. Technological advances and increased occupational specialization have enabled individual farming operations in developed countries to grow larger [15], while improving yields of field crops on a per hectare basis [16]. Mechanization, effective pesticides and herbicides, improved transportation infrastructure, and advanced crop genetics (including GE crops) have all contributed to higher levels of efficiency in producing crops. The high cost of discovering and developing advanced agricultural technologies to meet grower needs; assessing their food, feed, and environmental risk; and meeting regulatory requirements has also led to the consolidation of companies that develop and supply agricultural technology solutions (e.g., seed, machinery, pesticides, and fertilizer) [17]. The benefits of increased scale and technological capability are not unique to agriculture but are shared by many industries from healthcare to food retailing [18,19]. A separate issue commonly misattributed to company consolidation is patent coverage for GE crops. Counter to popular belief, patents for crop varieties have been granted since the 1930s to encourage investment in crop improvement, and they have simply been adapted to recent advances in crop breeding [20].

Historical Attributes of Agriculture

It is also noteworthy that some characteristics often attributed to modern agriculture are actually not unique but rather related to scale. One claimed disadvantage of modern agriculture is the planting of like crop plants together (monoculture). Although field sizes have increased, monoculture is as old as agriculture itself and even mentioned in the Old Testament: 'Do not plant your field with two kinds of seed' [21]. Even most home gardeners group their vegetable plants by species to enable efficient care and harvest (similar to commercial farmers).

Crop rotation of monocultures is the common practice of many modern and classical agricultural systems where an individual monocultured field is rotated to a different monocultured crop in alternate growing cycles (e.g., maize–soybean rotation) to disrupt pest life cycles and achieve other agronomic benefits [22]. Both permaculture and cultivation of annual crops have been common in agriculture for millennia [23]. Farmers today grow perennial crops such as fruit trees and grapes along with annual crops such as wheat and maize, and GE traits have been used to improve both types of crops (e.g., insect-resistant maize and ringspot-resistant papaya; Box 2) [24,25].

Box 2. Ringspot-Resistant GE Papaya

The major papaya production area of Hawaii, Puna, was initially infected with the devastating ringspot virus in 1992, and the entire area was severely infected within 5 years, causing farmers to abandon orchards with high infection rates [26]. Production in the Puna region, where 95% of Hawaii's papayas were grown, was cut in half within 6 years, while the quality of the remaining fruit was poorer. Furthermore, only three of eight packing houses remained open in 1998, thereby affecting local employment. GE ringspot-virus resistant papaya (Figure I) was first distributed to growers in 1998, and by 2004, the resistant Rainbow variety of papaya accounted for 88% of the planted area (with the remaining area supplying the Japan non-GMO market enabled by a buffer of surrounding GE ringspot-free plantings). GE technology is widely credited with saving the Hawaiian papaya industry, but its adoption globally has been hampered by regulatory barriers and consumer opposition to GE crops [27].

Trends in Plant Science

Figure I. Papaya Ringspot Virus. Ringspot-susceptible (left) and GE ringspot-resistant (right) papaya. Courtesy of S. Ferreira, copyright free.

In addition, the evolutionary adaptation of agricultural pests (pest resistance) is a well-characterized and commonly observed response to control practices linked to both the scale of agriculture and cropping practices [28]. Pest resistance is technology agnostic, occurring to synthetic and natural pesticides as well as to GE crops. Adaptation even occurs to cultural control techniques. For example, physiological and behavioral changes have been observed in populations of both northern and western corn rootworm in response to maize–soybean crop rotation (designed to break the pest cycle). In one species, the adaptation is extended diapause (dormancy) in eggs laid in the soil beneath maize plants that do not hatch until 2 years later, exactly when maize is replanted after the rotation to soybean [29]. In the second species, the adaptation is laying eggs in fields currently planted to soybean that hatch the following season when maize is replanted [30]. Hessian fly resistance in wheat is an example where different native (non-GE) host-plant resistance traits must be rotated over time to manage the pest as it adapts to each trait [31].

Finally, three additional misconceptions concerning perceived unique risks of modern agriculture and GE crops are related to (i) GE traits creating greater risk of a crop becoming a weed; (ii) the risk of pollen flow from crops to wild relatives; and (iii) the risk of these wild relatives becoming weedier due to trait transfer. First, crop plants have always had the potential to cross-pollinate with sexually compatible wild relatives and thus transfer selected crop traits to these wild relatives, potentially providing a selective advantage. Second, insect-resistance and herbicide-tolerance traits have been developed with non-GE breeding techniques (e.g., Hessian fly resistant wheat, European corn borer-resistant maize, and imidazolinone herbicide-tolerant crops) [31–33] (Box 3). It is also noteworthy that sexually compatible non-GE varieties

Box 3. Non-GE Imidazolinone-Tolerant Crops, Pollen Flow, and Weediness of Wild Relatives

Imidazolinones are a class of synthetic organic herbicides that inhibit acetohydroxyacid synthase (AHAS) that is a critical enzyme in the biosynthetic pathway of branched-chain amino acids in plants. Non-GE imidazolinone herbicide-tolerant maize, wheat, rice, oilseed rape, and sunflower were developed through mutagenesis of the gene expressing the target AHAS enzyme and selection for plants expressing an insensitive variant [33]. While crops such as maize do not have the attributes of weeds and are not adapted to survive outside human care [35], volunteer maize can certainly be considered a weed within fields rotated to another crop [34]. Thus, imidazolinone-tolerant maize volunteering in another imidazolinone-tolerant crop predictably requires use of an herbicide from a different class of chemicals or other control measures. The increased use of imidazolinone herbicides in response to cultivation of tolerant crops also increased the use of this class of herbicides contributing to selection pressure for the evolution of resistant weeds [36]. Furthermore, the cross-pollination of imidazolinone-tolerant cultivated rice with a weedy relative (red rice) resulted in populations of weeds tolerant to imidazolinone herbicides (Figure I), again requiring use of herbicides from different chemical classes or alternative measures to control this weed [37].

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Figure I. Imidazolinone-Resistant Weedy Red Rice Present in a Non-GE Imidazolinone-Tolerant Hybrid Rice Field near Midland, LA. The resistant weedy rice is in a field that was planted to non-GE imidazolinone-tolerant hybrid rice for four consecutive years. The resistance is due to outcrossing and dormant seed survival, germination, and establishment from shattered hybrid rice from consecutive years of production. Photograph taken by Eric Webster (weed scientist, LSU AgCenter) and reproduced here with his permission.

and crop types have coexisted for a very long time, requiring farmers to cooperate and isolate value-added crops that lose quality when outcrossed (e.g., sweet corn pollinated by field corn has reduced quality) [34]. Thus, many characteristics singled out to describe modern agriculture (and GE crops) are actually not unique, with the scale of modern agriculture truly being the discriminating attribute.

Agriculture Is Environmentally Disruptive

Although many of the aforementioned attributes of agriculture are not new, they are still highly disruptive to the in-field environment. Growing one or a few crop species over large land areas in simplified agroecosystems is disruptive of native habitats and the biodiversity that they often bring [38]. The same crop rotation that disrupts pest cycles also disrupts the cycles of non-pest and beneficial organisms. Although some have advocated for adapting agricultural practices to ‘share’ the agricultural ecosystem and improve biodiversity in the field at the expense of crop yield, most scientists agree that ‘sparing’ native habitats through higher agricultural production on fewer acres often creates the optimum biodiversity on a landscape scale [39–42]. Thus, technologies that increase harvestable yield can address both the increased food, feed, and fiber needs of a growing population and environmental conservation through land sparing. It is this intensive and highly disrupted agroecosystem designed to efficiently provide food, feed, and fiber that provides the context for GE crop technologies.

Risks of GE Crops

Plausible Risks of GE Crops

In the context of modern and historical agricultural development, GE crops potentially possess some quantitatively unique attributes that could present risk. Traits in non-GE crops have historically been generated through selection for random mutations, purposeful untargeted mutagenesis with radiation and chemicals, and introgression of genes from cultivated and wild crop relatives (sometimes without a history of safe use), whereas GE technology allows for movement of genes from a greater taxonomic range into crop plants [43,44]. Although a greater palette of genetic material is available, GE technology is distinguished from most traditional crop breeding methods by a much greater understanding of the genetic changes and the mechanism of achieving the desired phenotypic traits [45]. This greater precision and understanding allows potential risks to be assessed for new traits in GE crops that cannot easily be assessed for comparable non-GE traits (e.g., native host-plant pest resistance versus insect-resistant GE crops). These assessments include investigation of potential unintended harmful effects of the transgene products.

Characterization of Transgene Products

Although new conventional crop varieties and non-GE traits are often accompanied by new alleles and genes that produce proteins that may be novel in a crop, these are often uncharacterized, even when the source organism does not have a history of safe consumption [44,46]. In contrast, the amino acid sequence and mechanism of action for existing transgenic proteins in commercially grown crops are well characterized. This greater knowledge allows these proteins to be assessed for both nontarget toxicity and allergenicity [47,48]. Similarly, the mode of action for transgenic proteins that modulate chemical or biochemical pathways (e.g., enzymes) or gene expression (e.g., transcription factors) is known, so potential nontarget effects can be hypothesized and investigated for potential adverse outcomes [49]. Although not proteins, small interfering RNA (siRNA) produced by transgenes has a known mechanism of suppressing expression of specific genes, and the specificity of this suppression can be evaluated using bioinformatic methods [50].

Economic Risks

Although this discussion focuses primarily on food, feed, and environmental risk assessment, it is acknowledged that GE crop technology is considered economically disruptive in that it has the potential to displace older technologies (e.g., conventional crops, synthetic pesticides, and selective herbicides) [51]. Although this type of economic disruption is not unique to agriculture (e.g., smart phones displacing landlines and desktop computers), GE crops may create economic risks for some competing technology providers. Furthermore, the societal resistance to this technology by some trading partners and the public may result in adverse economic impacts, including reduced rates of adoption of innovative technology [52].

Non-safety or Non-GE-Specific Risks

As touched on earlier, several risks commonly attributed to GE crops are really not new or unique in GE crops. For example, pests have always adapted to pest control strategies and weeds have always become resistant to herbicides [53]. Irrespective of GE crops, overuse of any single tool to combat pests and weeds favors the development of resistance due to high evolutionary pressure, and GE technology is not immune to this force of nature any more than antibiotics are immune to bacterial resistance when they are overused. The only way to ensure that resistance does not occur is to not use the tool, which means that no benefit is ever realized (e.g., hypothetically banning antibiotics). For pest and weed control, resistance is not a safety risk per se but rather an economic risk due to lost efficacy of the tools.

Some have also contended that GE technology reduces both agroecosystem biodiversity and crop biodiversity. Agroecosystems by their very nature are not biodiverse but rather optimized for production of food, feed, and fiber [38]. Although adverse landscape effects should be minimized, the best way to accomplish this in most situations is to spare natural habitats through higher agricultural yield on less land [40,41,54]. Furthermore, GE insect-tolerance traits have brought environmental benefits over the insecticides they often replace and are less likely to affect beneficial species [11]. In terms of crop genetic biodiversity, crop breeding introduces and selects for traits that favor productivity goals or desired characteristics. GE traits are added to the background genome of the crop plant and then introgressed into the diversity of varieties that have always been developed to optimize yield under different growing conditions [38]. This technically increases genetic diversity by adding to the crop gene pool (Box 4).

Finally, GE crop opponents often attribute the increase in farm size and consolidation of the agroindustry to this technology, when in fact, agriculture has a very long history of consolidation (as have many industries) driven by an array of technologies and economic forces (e.g., machinery, pesticides, government regulation, new breeding technologies, etc.) [17]. As with weed and pest resistance, this is an economic or ideological issue and not a safety risk.

Box 4. Texas Cytoplasm

A male-sterility trait, based on mitochondrial gene rearrangements and mutations (commonly referred to as Texas cytoplasm), was widely incorporated into North American maize hybrids in the 1950s and 1960s to facilitate hybrid seed production (85% of acres in 1969 and 1970) [55]. Weather conditions in the early 1970s favored development of southern corn leaf blight (Figure I) revealing the unintended susceptibility of maize varieties containing the Texas cytoplasm mitochondrial trait to this disease. The result was an estimated 15% crop loss at a cost of approximately US $1 billion dollars (>US$6 billion today). Unlike current GE crops, which generally add genes to the genome of a crop, this non-GE male-sterility trait was based on the replacement of the mitochondrial genome in maize. As such, the loss of crop biodiversity with this traditional breeding tool was of a much higher magnitude compared with any existing GE crop.

Figure I. Maize Infected with Southern Corn Leaf Blight. Photograph reproduced here with permission from Pioneer Hi-Bred International.

Misattributed Risks

Although the potentially wider taxonomic sourcing of transgenes could be expected to allow for a greater array of expressed transgene products, the accompanying greater understanding of GE traits and their mechanism makes unexpected effects less likely than those anticipated and observed for non-GE breeding methods [45,56–58]. Likewise, the limited genetic disruption expected and observed for transgenesis, compared with the random mutagenesis that accompanies several non-GE breeding methods, reduces unintended genetic changes in GE crops versus non-GE crops [43]. It is also noteworthy that GE traits are introgressed into many different varieties within a crop, and like non-GE varieties, breeders evaluate each variety for trait efficacy and agronomic performance before commercial release. Therefore, similar to the assertion of some misinformed groups that vaccines cause autism [59], many of the assertions concerning the risks of GE crops are not supported by the scientific evidence; rather, they are claimed based on the ideological belief that 'natural' equates with safe [60]. This belief persists even though data support that endogenous plant constituents are just as likely to cause cancer as synthetic chemicals, and that the most toxic substances known to humans occur naturally [61,62]. This misconception also does not consider that gene transfer among taxonomically distant species does occur in nature [63] (see Box 5, sweet potato example) and that transgenesis actually mimics these natural processes (e.g., use of agrobacteria to transform crops, the reliance on native DNA repair mechanisms and DNA expression, heritability of DNA, etc.) [64].

Benefits of GE Crops in the Context of Non-GE Agriculture

Environmental Benefits

Most commercialized GE traits are designed to protect yield. Pest-resistance traits reduce damage by insects, viruses, and fungi, whereas herbicide-tolerance traits allow additional weed control options. More recently, drought-tolerance traits allow crops to use water more effectively. These traits replace or augment insecticides and fungicides, crop-selective herbicides, and irrigation, respectively [67]. By protecting yield, fewer hectares of cropland are required to produce the same amount of crop, thereby reducing the amount of native habitat that must be converted to farmland to support the human demand for food, feed, and fiber. Pest-resistance traits have also been found more environmentally benign than most pesticides due to their increased pest specificity, lower off-site movement and effects, and elimination of manufacture, containerization, transport, application, and disposal activities (that contribute to climate change) [11]. It has been reported that the adoption of crops developed with biotechnology has resulted in decreased carbon emissions that are estimated to be equivalent to the removal of almost 12 million cars from the road for 1 year because of decreased fuel usage and tillage [11]. Regional suppression of insect pests due to widespread adoption of insect-resistant GE crops has also reduced pesticide use on non-GE crops by lowering the overall pest pressure in a wide geographic area [68–70]. Furthermore, in some cases, overall yield increases have been realized compared with alternative practices due to the improved economics of traits compared with pesticide applications (e.g., alternative control options were generally not economical for

Box 5. Ancient GE Sweet Potato

Agrobacterium tumefaciens is a common vector used to transfer transgenes to GE crops. This bacterium was chosen because of its natural ability to insert its genes in host-plant non-reproductive (somatic) cells, forming galls that it inhabits [65]. Because GE crop plants are regenerated from single somatic cells grown in tissue culture, *Agrobacterium*-mediated transformational changes in the DNA are replicated in the reproductive cells of the regenerated plant, allowing the genetic changes to be inherited. Recently, the ancient transfer of genes from *Agrobacterium* to the sweet potato genome was discovered [63]. These transgenes are found in all sweet potato cultivars thus investigated. This horizontal gene transfer is not unique to sweet potato and is now believed to be a contributor to plant evolution [66].

European corn borer control in field corn) or the lack of alternative control measures (e.g., ringspot control in papaya) requiring fewer hectares to produce the same crop [4]. Herbicide-tolerance traits also provide an improved level of weed control and application flexibility to growers that favor greater adoption of conservation tillage practices that reduce soil erosion and runoff into waterways [71].

Health Benefits

In addition to environmental benefits, the reduction in pesticide use (and increased use of safer herbicides) has been credited with health benefits for applicators in developing countries where use of personal protective equipment may be inconsistent [72–74]. Unprecedented protection from insect damage provided by GE insect-resistance traits in maize has also resulted in lower concentrations of toxic, mutagenic, and carcinogenic mycotoxins due to a reduction in pest-induced plant wounds that are often colonized by the fungi that produce these toxins [24,75,76]. Furthermore, the GE non-browning trait in white potatoes decreases an undesirable byproduct of frying (acrylamide) that may be carcinogenic at very high exposure rates [77,78]. Finally, GE traits that increase the quantities of healthy oils or that produce critical nutrients are being introduced to improve human health [79].

Economic Benefits

GE traits also bring economic benefits for farmers and consumers [5]. Efficiencies and reduced agricultural production costs economically benefit both growers and consumers by making food more affordable [80]. The addition of GE tools can also be incorporated into integrated pest management and integrated weed management programs to preserve control options over time (durability). One unique benefit of GE approaches to insect control is the ability to achieve high doses relative to pest susceptibility and the ability to pyramid traits, each of which improves the durability of GE traits compared with traditional insecticides [81].

Risks of Not Considering Benefits for GE Crops

Context and Risk

It is important to consider the agricultural context when assessing the risks of GE crops. The appropriate comparator for GE crops is the mainstream agricultural system into which this technology is introduced [34]. Consideration of the appropriate context is important in that some regard the improvement of this common agricultural system a risk because it may inhibit the adoption of alternative systems (e.g., organic or polyculture production). This is analogous to the risk that introducing cleaner emission technology for combustion automobile engines contributes to continued use of combustion engines, thereby limiting the adoption of bicycles or electric cars [82]. Therefore, the unique risks of GE crops can be anticipated and are generally restricted to potential nontarget effects of the transgene products/traits (e.g., toxicity, allergenicity, and plausible adverse effects on crop composition). In general, the risk of unexpected adverse effects for GE crops is lower than that of traditional breeding due to greater knowledge of GE traits [43,45,58]. Economic risks for alternative technology providers is also not unique to GE crops but rather the nature of technological advancement.

Benefits

Yield protection and enhancement for specific GE crops reduces pressure on native habitats and brings economic gains to growers and reduced food costs to consumers [39,80]. Pesticidal GE traits often provide superior pest control compared with alternative technologies while being more environmentally benign and less hazardous to nontarget organisms, including humans [11,72]. In addition, exposure to dangerous mycotoxins in insect-resistant GE maize by humans and livestock is reduced [24]. Herbicide-tolerant GE crops often resulted in

Box 6. Coffee: Paradox of Not Considering Benefits in Risk Assessment

The health benefits of coffee consumption have been studied and include a 'probable decreased risk of breast, colorectal, colon, endometrial, and prostate cancer, cardiovascular disease and mortality, Parkinson's disease, and type-2 diabetes' [85]. Recently, under California's Safe Drinking Water and Toxic Enforcement Act, also known as Proposition 65, the Council for Education and Research on Toxics sued the coffee industry and won a court decision requiring coffee to be labeled with a cancer warning because it contains very low levels of acrylamide produced during roasting from the naturally occurring precursors sucrose and asparagine [86] (https://www.popsci.com/california-coffee-cancer-warning). By not considering the benefits of coffee, particularly in reducing cancer rates [87], this proposed cancer warning label could reduce coffee consumption and consequently result in increased rates of cancer (https://www.hsph.harvard.edu/nutritionsource/2018/04/02/coffee-warning-label-conflicts-with-public-health-guidance/).

replacement of other herbicides with glyphosate, a herbicide that has an excellent human and environmental safety profile [83]. Conservation tillage was also more widely integrated into farming operations due to the efficacy and flexibility of glyphosate. GE crops with improved nutrition and safety have also been developed [79]. Thus, specific GE crops can bring health, environmental, and economic benefits to society.

Concluding Remarks: Risk Arising from Rejection

Societal rejection and risk-disproportionate regulation of GE crops increase development costs, potentially depriving society of the benefits of this technology. Current regulatory testing is complex, resource intensive, and expensive and therefore largely restricts development of this technology to multinational corporations working on solutions for widespread problems within large-hectare crops in developed countries, while disadvantaging small developers and academic contributions to more narrow problems in developing countries [9]. Overly precautionary regulation also implies that the risks are high or uncertain, potentially contributing to public rejection of beneficial technology (see Box 6, coffee label example). Furthermore, GE technology may be rejected by countries fearing lost exports due to imagined safety risks by an economically important importer [80]. Large commercial buyers of a specific crop have also rejected GE technology, fearing consumer avoidance (e.g., rejection of GE pest-resistant white potatoes by McDonald's), leading to redeployment of older technologies (e.g., substantial pesticide use) [84]. There are real consequences to rejecting any technology without considering the benefits it brings to society. GE crops are a good example where the science is clear on both the very low risk and the substantial benefits. It is therefore imperative that benefits, and the risk of forgoing these benefits, be included in the risk assessment of GE crops so that society can benefit from their judicious incorporation in agricultural systems and the food chain. This is especially important as the world population continues to grow and the effects of climate change are felt across the globe (see Outstanding Questions).

Outstanding Questions

How can a better bridge between scientific understanding and societal impressions be built?

What activities will help connect the realities of food production with the billions of consumers who depend on it?

How can the evidenced risks and benefits of genetically engineered crops be better communicated?

Disclaimer Statement

R.A.H., M.Z. N.P.S., F.C., and B.D. are employed by Corteva Agriscience^{TM}, Agriculture Division of DowDuPont^{TM}, which develops and markets genetically engineered seed.

References

1. Turner, P.J. *et al.* (2015) Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J. Allergy Clin. Immunol.* 136, 376–381
2. Fenner, F. (1982) Global eradication of smallpox. *Rev. Infect. Dis.* 4, 916–930
3. National Academies of Sciences, Engineering, and Medicine (2016) *Genetically Engineered Crops: Experiences and Prospects,* The National Academies Press
4. Klümper, W. and Qaim, M. (2014) A meta-analysis of the impacts of genetically modified crops. *PLoS One* 9, 1–7 e111629
5. James, C. (2016) Global status of commercialized biotech/GM crops: 2016. *ISAAA Brief* No. 52, ISAAA
6. Smyth, S.J. (2017) Genetically modified crops, regulatory delays, and international trade. *Food Energy Secur.* 6, 78–86
7. Bennett, A.B. *et al.* (2013) Agricultural biotechnology: economics, environment, ethics, and the future. *Annu. Rev. Environ. Resour.* 38, 249–279
8. Wesseler, J. and Zilberman, D. (2014) The economic power of the Golden Rice opposition. *Environ. Dev. Econ.* 19, 724–742

9. Bradford, K.J. *et al.* (2005) Regulating transgenic crops sensibly: lessons from plant breeding, biotechnology and genomics. *Nat. Biotechnol.* 23, 439–444
10. Masip, G. *et al.* (2013) Paradoxical EU agricultural policies on genetically engineered crops. *Trends Plant Sci.* 18, 312–324
11. Brookes, G. and Barfoot, P. (2017) Environmental impacts of genetically modified (GM) crop use 1996–2015: impacts on pesticide use and carbon emissions. *GM Crops Food* 8, 117–147
12. Goldewijk, K.K. (2001) Estimating global land use change over the past 300 years: the HYDE Database. *Global Biogeochem. Cycles* 15, 417–433
13. United Nations (2015) World population prospects. The 2015 revision, key findings and advance tables. Working Paper No. ESA/P/WP .241, United Nations, Department of Economic and Social Affairs
14. Food and Agriculture Organization of the United Nations (2009) *How to Feed the World in 2050*. Discussion paper. High-level expert forum, The Food and Agricultural Organization
15. Lowder, S.K. *et al.* (2016) The number, size, and distribution of farms, smallholder farms, and family farms worldwide. *World Dev.* 87, 16–29
16. Ray, D.K. *et al.* (2013) Yield trends are insufficient to double global crop production by 2050. *PLoS One* 8, 1–8 e66428
17. Fuglie, K.O. *et al.* (2011) *Research Investments and Market Structure in the Food Processing, Agricultural Input, and Biofuel Industries Worldwide,* US Department of Agriculture, Economic Research Service
18. Chakraborty, R. *et al.* (2014) Market consolidation and pricing developments in grocery retailing: a case study. In *The Analysis of Competition Policy and Sectoral Regulation*, pp. 3–29, World Scientific
19. Connor, R.A. *et al.* (1998) The effects of market concentration and horizontal mergers on hospital costs and prices. *Int. J. Econ. Bus.* 5, 159–180
20. Pardey, P.G. *et al.* (2013) The evolving landscape of plant varietal rights in the United States, 1930–2008. *Nat. Biotechnol.* 31, 25–29
21. Hays, J.D. (2001) Applying the Old Testament law today. *Bibliotheca Sacra* 158, 21–35
22. Bullock, D.G. (1992) Crop rotation. *Crit. Rev. Plant Sci.* 11, 309–326
23. Zohari, D. (1986) The origin and early spread of agriculture in the Old World. In *Developments in Agricultural and Managed Forest Ecology*, pp. 3–20, Elsevier
24. Pellegrino, E. *et al.* (2018) Impact of genetically engineered maize on agronomic, environmental and toxicological traits: a meta-analysis of 21 years of field data. *Sci. Rep.* 8, 1–12
25. Mendoza, E.M.T. *et al.* (2008) Recent advances in the development of transgenic papaya technology. *Biotechnol. Annu. Rev.* 14, 423–462
26. Gonsalves, D. (2006) Transgenic papaya: development, release, impact and challenges. *Adv. Virus Res.* 67, 317–354
27. Fermin, G.A. *et al.* (2010) CP-transgenic and non-transgenic approaches for the control of papaya ringspot: current situation and challenges. *Transgenic Plant J.* 4, 1–15
28. Denholm, I. and Rowland, M. (1992) Tactics for managing pesticide resistance in arthropods: theory and practice. *Annu. Rev. Entomol.* 37, 91–112
29. Krysan, J.L. *et al.* (1986) Two years before the hatch: rootworms adapt to crop rotation. *Bull. Entomol. Soc. Am.* 32, 250–253
30. Levine, E. *et al.* (2002) Adaptation of the western corn rootworm to crop rotation: evolution of a new strain in response to a management practice. *Am. Entomol.* 48, 94–107
31. Foster, J. *et al.* (1991) Effectiveness of deploying single gene resistances in wheat for controlling damage by the Hessian fly (Diptera: Cecidomyiidae). *Environ. Entomol.* 20, 964–969
32. Abel, C.A. *et al.* (2001) Registration of GEMS-0001 maize germplasm resistant to leaf blade, leaf sheath, and collar feeding by European corn borer. *Crop Sci.* 41, 1651–1652
33. Tan, S. *et al.* (2005) Imidazolinone-tolerant crops: history, current status and future. *Pest Manag. Sci.* 61, 246–257
34. Conner, A.J. *et al.* (2003) The release of genetically modified crops into the environment. *Plant J.* 33, 19–46
35. Raybould, A. *et al.* (2012) Assessing the ecological risks from the persistence and spread of feral populations of insect-resistant transgenic maize. *Transgenic Res.* 21, 655–664
36. Tranel, P.J. and Wright, T.R. (2002) Resistance of weeds to ALS-inhibiting herbicides: what have we learned? *Weed Sci.* 50, 700–712
37. Roso, A.C. *et al.* (2010) Regional scale distribution of imidazolinone herbicide-resistant alleles in red rice (*Oryza sativa* L.) determined through SNP markers. *Field Crops Res.* 119, 175–182
38. Ammann, K. (2005) Effects of biotechnology on biodiversity: herbicide-tolerant and insect-resistant GM crops. *Trends Biotechnol.* 23, 388–394
39. Phalan, B. *et al.* (2011) Reconciling food production and biodiversity conservation: land sharing and land sparing compared. *Science* 333, 1289–1291
40. Egan, J.F. and Mortensen, D.A. (2012) A comparison of land-sharing and land-sparing strategies for plant richness conservation in agricultural landscapes. *Ecol. Appl.* 22, 459–471
41. Balmford, A. *et al.* (2005) Sparing land for nature: exploring the potential impact of changes in agricultural yield on the area needed for crop production. *Glob. Change Biol.* 11, 1594–1605
42. Williams, D.R. *et al.* (2018) Carbon storage and land-use strategies in agricultural landscapes across three continents. *Curr. Biol.* 28, 2500–2505
43. Schnell, J. *et al.* (2015) A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments. *Transgenic Res.* 24, 1–17
44. Conko, G. *et al.* (2016) A risk-based approach to the regulation of genetically engineered organisms. *Nat. Biotechnol.* 34, 493–503
45. Herman, R.A. and Price, W.D. (2013) Unintended compositional changes in genetically modified (GM) crops: 20 years of research. *J. Agric. Food Chem.* 61, 11695–11701
46. Osman, S.F. *et al.* (1978) Glycoalkaloid composition of wild and cultivated tuber-bearing *Solanum* species of potential value in potato breeding programs. *J. Agric. Food Chem.* 26, 1246–1248
47. Delaney, B. *et al.* (2008) Evaluation of protein safety in the context of agricultural biotechnology. *Food Chem. Toxicol.* 46, S71–S97
48. Herman, R.A. and Ladics, G.S. (2018) Allergenic sensitization versus elicitation risk criteria for novel food proteins. *Regul. Toxicol. Pharmacol.* 94, 283–285
49. Parrott, W. *et al.* (2010) Application of food and feed safety assessment principles to evaluate transgenic approaches to gene modulation in crops. *Food Chem. Toxicol.* 48, 1773–1790
50. Whyard, S. *et al.* (2009) Ingested double-stranded RNAs can act as species-specific insecticides. *Insect Biochem. Mol. Biol.* 39, 824–832
51. Qaim, M. (2009) The economics of genetically modified crops. *Annu. Rev. Resour. Econ.* 1, 665–694
52. Kerr, W.A. (1999) Genetically modified organisms, consumer scepticism and trade law: implications for the organisation of international supply chains. *Supply Chain Manag.* 4, 67–74
53. Palumbi, S.R. (2001) Humans as the world's greatest evolutionary force. *Science* 293, 1786–1790
54. Phalan, B. *et al.* (2016) How can higher-yield farming help to spare nature? *Science* 351, 450–451
55. Bruns, H.A. (2017) Southern corn leaf blight: a story worth retelling. *Agron. J.* 109, 1218–1224
56. Herman, R.A. *et al.* (2017) Stacking transgenic event DAS-Ø15Ø7-1 alters maize composition less than traditional breeding. *Plant Biotechnol. J.* 15, 1264–1272
57. Hill, R.C. *et al.* (2017) Transgenesis affects endogenous soybean allergen levels less than traditional breeding. *Regul. Toxicol. Pharmacol.* 89, 70–73
58. Van Eenennaam, A. and Young, A. (2014) Prevalence and impacts of genetically engineered feedstuffs on livestock populations. *J. Anim. Sci.* 92, 4255–4278

59. Taylor, L.E. *et al.* (2014) Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine* 32, 3623–3629
60. Sagoff, M. (2001) Genetic engineering and the concept of the natural. *Philos. Public Policy Q.* 21, 2–10
61. Ames, B.N. *et al.* (1990) Dietary pesticides (99.99% all natural). *Proc. Natl. Acad. Sci. U. S. A.* 87, 7777–7781
62. Middlebrook, J.L. and Franz, D.R. (1997) Botulinum toxins. In *Medical Aspects of Chemical and Biological Warfare*, pp. 643–654, Borden Institute
63. Kyndt, T. *et al.* (2015) The genome of cultivated sweet potato contains *Agrobacterium* T-DNAs with expressed genes: an example of a naturally transgenic food crop. *Proc. Natl. Acad. Sci. U. S. A.* 112, 5844–5849
64. Tzfira, T. and Citovsky, V. (2006) Agrobacterium-mediated genetic transformation of plants: biology and biotechnology. *Curr. Opin. Biotechnol.* 17, 147–154
65. Larebeke, N.V. *et al.* (1974) Large plasmid in *Agrobacterium tumefaciens* essential for crown gall-inducing ability. *Nature* 252, 169–170
66. Quispe-Huamanquispe, D.G. *et al.* (2017) Horizontal gene transfer contributes to plant evolution: the case of *Agrobacterium* T-DNAs. *Front. Plant Sci.* 8, 1–6
67. Paul, M.J. *et al.* (2018) Are GM crops for yield and resilience possible? *Trends Plant Sci.* 23, 10–16
68. Dively, G.P. *et al.* (2018) Regional pest suppression associated with widespread Bt maize adoption benefits vegetable growers. *Proc. Natl. Acad. Sci. U. S. A.* 115, 3320–3325
69. Hutchison, W.D. *et al.* (2010) Areawide suppression of European corn borer with Bt maize reaps savings to non-Bt maize growers. *Science* 330, 222–225
70. Wan, P. *et al.* (2012) The halo effect: suppression of pink bollworm on non-Bt cotton by Bt cotton in China. *PLoS One* 7, 1–6 e42004
71. Givens, W.A. *et al.* (2009) Survey of tillage trends following the adoption of glyphosate-resistant crops. *Weed Technol.* 23, 150–155
72. Pray, C.E. *et al.* (2002) Five years of Bt cotton in China: the benefits continue. *Plant J.* 31, 423–430
73. Hossain, F. *et al.* (2004) Genetically modified cotton and farmers' health in China. *Int. J. Occup. Environ. Health* 10, 296–303
74. Kouser, S. and Qaim, M. (2011) Impact of Bt cotton on pesticide poisoning in smallholder agriculture: a panel data analysis. *Ecol. Econ.* 70, 2105–2113
75. Parrott, W. (2010) Genetically modified myths and realities. *New Biotechnol.* 27, 545–551
76. Marasas, W.F. (1995) Fumonisins: their implications for human and animal health. *Nat. Toxins* 3, 193–198
77. Rommens, C.M. *et al.* (2008) Low-acrylamide French fries and potato chips. *Plant Biotechnol. J.* 6, 843–853
78. Waltz, E. (2015) USDA approves next-generation GM potato. *Nat. Biotechnol.* 33, 12–14
79. Hefferon, K.L. (2018) Crops with improved nutritional content though agricultural biotechnology. In *Plant Micronutrient Use Efficiency*, pp. 279–294, Elsevier
80. Anderson, K. (2010) Economic impacts of policies affecting crop biotechnology and trade. *New Biotechnol.* 27, 558–564
81. Tabashnik, B.E. *et al.* (2013) Insect resistance to Bt crops: lessons from the first billion acres. *Nat. Biotechnol.* 31, 510–521
82. Herman, R.A. and Raybould, A. (2013) Invoking ideology in the promotion of ecological risk assessment for GM crops. *Trends Biotechnol.* 31, 217–218
83. Green, J.M. (2012) The benefits of herbicide-resistant crops. *Pest Manag. Sci.* 68, 1323–1331
84. Kaniewski, W.K. and Thomas, P.E. (2004) The potato story. *AgBioForum* 7, 41–46
85. Grosso, G. *et al.* (2017) Coffee, caffeine, and health outcomes: an umbrella review. *Annu. Rev. Nutr.* 37, 131–156
86. Bagdonaite, K. *et al.* (2008) Determination of acrylamide during roasting of coffee. *J. Agric. Food Chem.* 56, 6081–6086
87. Sado, J. *et al.* (2017) Association between coffee consumption and all-sites cancer incidence and mortality. *Cancer Sci.* 108, 20792087