Review

Agricultural GMOs—What We Know and Where Scientists Disagree

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Abstract: Population growth, climate change, and increasing human impact on land and aquatic systems all pose significant challenges for current agricultural practices. Genetic engineering is a tool to speed up breeding for new varieties, which can help farmers and agricultural systems adapt to rapidly changing physical growing conditions, technology, and global markets. We review the current scientific literature and present the potential of genetically modified organisms (GMOs) from the perspectives of various stakeholders. GMOs increase yields, lower costs, and reduce the land and environmental footprint of agriculture. The benefits of this technology are shared among innovators, farmers, and consumers. Developing countries and poor farmers gain substantially from GMOs. Agricultural biotechnology is diverse, with many applications having different potential impacts. Its regulation needs to balance benefits and risks for each application. Excessive precaution prevents significant benefits. Increasing access to the technology and avoidance of excessive regulation will allow it to reach its potential.

Keywords: genetic engineering; biotechnology; intellectual property; sustainability; climate change

1. Introduction

Genetic engineering (GE) has the potential to address some of the major challenges of our time, including food security, climate change adaptation, and environmental sustainability. It provides new tools and capacities to increase agricultural productivity, reduce its environmental footprint, feed growing populations in developing countries, and empower disadvantaged groups. At the same time, genetic engineering in agriculture has encountered fierce resistance by various ideological groups and powerful corporations and governments: the European Commission instituted a mandatory GMO label on food products; many of its members, including France and Germany, have banned the growing of GMOs entirely; India, while allowing for GE cotton to be grown, has refused to authorize GE rice varieties [1–5]. This has led to a regulatory system that constrains the introduction of new varieties based on transgenic technologies, particularly in developing countries that would benefit most from them.

This article aims to review current knowledge on GE in agriculture and its potential implications for sustainable development, defined as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs" [6]. The literature on the economics of sustainable development suggests that GE can play an important role in strategies towards this goal in agriculture, mainly by increasing yield per unit of output, reducing the use of pesticides and other chemicals, using land more efficiently, and reducing greenhouse gas emissions in the process of growing food. GE technologies that contribute to improved enzymes and more

efficient fermentation are important contributors to the bioeconomy and recycling of agricultural residues [7]. We will argue that much of the criticism of genetic engineering is unfounded, both on the natural science and the social science aspects. With sound regulation, we can overcome most concerns regarding GE in agriculture in order to allow the sustainable and equitable utilization of biotechnology.

We present the current evidence on GE impact for sustainability in the following structure. After a short overview of the technologies and their capabilities, we investigate the dimension of potential health effects of GMOs to humans, which seems to motivate much of the debate on the topic. In short, scientific consensus is that their consumption is at least as safe as conventional crop consumption, and no evidence that agricultural biotechnology poses unique or new risks has been found to date. In fact, evidence does exist of increased food safety in some cases. Following the health discussion, we touch on the dimension of environmental risks and opportunities posed by GMOs. We then proceed to explore existing evidence that biotechnology can actually increase productivity and improve the welfare of the poor, while reducing the environmental footprint of agriculture at the same time. We review findings on the impact of agricultural biotechnology both at the farm and aggregate levels, showing that it can enhance crop biodiversity, reduce greenhouse gas emissions from agriculture, and reduce other environmental side effects of current practices. This is followed by a discussion of the distributional effects and the political economy of GMOs, showing that the gains from agricultural biotechnology are shared between farmers, consumers and companies. Access to the benefits of a GE technology may be over-constrained by intellectual property considerations, and we find that access to technologies can be improved. However, in most situations, intellectual property constraints can be overcome to introduce new applications in orphan crops and crops that are consumed by the poor.

The major constraint for the utilization of biotechnology has been regulatory. The strict regulations of agricultural biotechnology were initially justified by high levels of uncertainty surrounding new technologies. However, we will show that this precautionary approach comes at a price, and that a more appropriate regulatory approach given current experience with these technologies should better balance benefits, costs and risks. As a last point, we discuss the topic of GMO labelling and its implications for the adoption rate of biotechnology and by extension for the potential of biotechnology to improve the sustainability of agriculture.

2. What Is Agricultural Biotechnology?

Nearly all food crops humans consume at present are different than their earliest natural ancestor. They have been manipulated and modified for millennia. Gathering and replanting seeds, farmers selected the plants more resistant to droughts and pest, and the ones yielding more than others. Mendel's discovery of the rules of inheritance ushered in an era of systematic genetic selection. As scientific capabilities improved, scientists have aimed to expand genetic variation artificially through methods like mutagenesis (use of radiation to produce new mutants) and more precise breeding programs. However, the transmission of hereditary traits was still confined within the species, usually within close varieties, as it used the plants' own reproductive mechanisms. The scope of traditional breeding was thus limited. The discovery of DNA in the 1950s opened new avenues for biologists. It provided understanding of the mechanisms behind the changes in properties of various species, and provided new tools for genetic improvement. Scientists were challenged with mapping their genomes, and linking performance and properties of organisms with their genetic makeup [3].

Agricultural scientists developed multiple approaches to take advantage of new scientific knowledge. They developed the use of molecular markers to identify properties of genetic materials of different organisms. They developed GE technologies, in particular transgenic methods (using agrobacterium or other methods) to transfer genes that convey certain traits among species. More recently, they developed technologies to edit genes, which means inserting or eliminating genes as well as transforming genes. The pool of potential new traits, traditionally limited by plant reproduction, is now much wider.

We believe GE technologies are an essential step in the evolution of crops. In a world with a rapidly increasing population to feed, facing increasing challenges posed by climate change, and with the desire to reduce the footprint of agriculture, crop varieties need to constantly change to face new realities and constraints. GE technologies are a way of achieving this, expanding the capabilities of agriculture while potentially reducing its monetary and environmental costs. One major advantage of GE is that it reduces the time it takes to develop a desired trait or variety. This is especially important in the context of climate change, where the speed of plant breeding may reduce the costs of adaptation.

Much of the social concern regarding GE technologies is about the safety of transgenic procedures and their unexpected side effects. Scientific developments and the regulatory process aim to minimize, or even eliminate, these side effects. We could not find evidence of mishaps with transgenic varieties that caused clear environmental or health damage. However, nothing is fool-proof, and a rational and robust regulatory regime will always have a role in the evaluation of new biotechnologies as they emerge.

While the concern about the safety of transgenic methods is understandable, it is important to compare the methods of genetic engineering with their alternatives. GE technologies are much more precise than traditional breeding or mutagenesis [8–10]. In traditional breeding, new varieties are developed by targeting observed phenotypes (expressions of genetic traits). Genetic changes and their phenotypical expressions are achieved through planned breeding, but the genotype (the actual genetic composition) of the new varieties is not controlled for. With GE, slight modifications are performed internally to control a specific aspect of plant performance. A desired phenotype is specified and targeted, and a precise genetic change is made specifically to achieve it, while the rest of the genotype is left unaltered. This means that the chances of unintended gene expressions in GMOs are lower than in varieties created via traditional breeding techniques.

GE applications are usually divided into three "generations". The first-generation traits are mostly utilized for pest control, either through resistance to pests (arthropods or fungi) or tolerance to herbicides. The second generation include traits that improve properties of crops (e.g., longer shelf life, enhanced nutritional value) or improve their capacity to withstand abiotic stresses (e.g., drought or flood tolerance). Third generation traits encode for the bio-synthesis of useful chemicals by plants. Two subgroups of these products are plant made pharmaceuticals (PMPs), such as proteins, reagents, and antibodies; and plant made industrial products (PMIPs) such as silk protein, elastin and collagen, bio-degradable plastic precursors, and fossil fuel alternatives [11–13]. A very small proportion of lab-proven traits are currently in commercial use. While Bennett et al. [13] identify more than one hundred traits, the costly regulations of agricultural biotechnology have prevented scientists from investing in field trials of many varieties with desirable traits.

Gene editing, or genome editing, is a relatively new form of GE that relies on species-specific nucleases (SSNs) to insert, knock out, or modify specific genes. It relies on a set of tools that include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) associated systems [9]. Of these, CRISPR-Cas9 is the most recent development and has been shown to be versatile as well as simpler and less expensive to implement than its predecessors [14]. Unlike ZFNs and TALENs, CRISPR has been shown to be efficient at modifying multiple genes in a single plant; this greatly increases the potential of the technology for engineering advantageous traits, such as pest resistance [9].

Gene editing has already been demonstrated on major crops, including—as of 2015—barley, maize, rice, soybean, sweet orange, tomato, and wheat [15]. Traits currently under investigation include, among others, herbicide resistance, drought tolerance, improved nutritional content, salt resistance, and resistance to biotic stress [16]. Because it is more precise and predictable than earlier technologies that relied on the introduction of transgenes, gene edited crops may prove to be more acceptable to the public than were earlier GMOs [10]. However, important questions remain regarding regulatory frameworks and public acceptance.

3. Human Health

We begin the review of the impacts of GE on sustainability with the dimension of human health. While discussions of sustainable development do not typically emphasize health concerns, they are a critical component of any debate on the traits of a food-related technology. Opponents of genetic engineering have frequently raised concerns about the impacts of GMOs on human health [17]. These concerns broadly fall into two categories: concerns about the consumption of GMOs, and concerns about the cultivation of GMOs. Both concerns seem unfounded by scientific literature.

Despite frequent claims to the contrary by anti-GMO advocacy groups, after decades of production, there is no clear evidence of harm to the health of consumers that has resulted from the consumption of GMO products. In a review of 1,783 studies on the safety of genetically engineered crops published over a 10-year period, Nicolia et al. [18] found no reports of significant hazards that were directly linked to GM crops. Similar conclusions are consistently drawn by other reviews [17,19]. Of the small number of studies that have purported to show risks to human health, all have either been retracted or have been shown to have methodological or other flaws [20]. To put the purported health risks of GMOs in a broader perspective, in 2012, food-borne illnesses in the USA led to 128,000 hospitalizations and 3000 deaths; in contrast, to date there have been none reported that have been linked to the consumption of GMOs [19].

A good example of the potential health benefit of GE crops is with Bt-maize. Bt crops are engineered to include a gene that encodes the production of Bt toxins, low toxicity insecticides naturally produced by the soil-dwelling bacterium *Bacillus thuringiensis* and used by conventional and organic growers by means of spraying. They are lethal to larvae of specific species, and only by ingestion. Thus, Bt crops target crop pests that attack them, resulting in less need for the use of more toxic insecticides which could remain on the food. Consumers benefit even further: increased pest-protection attributes serve to reduce levels of mycotoxins, metabolic byproducts of some fungi which attack the plants through the pest inflicted wounds [21]. One type of mycotoxins, aflatoxin, is a carcinogen that has been particularly associated with liver cancer. One study in China of goods sold in local markets found average levels of aflatoxin in several crops that were higher than what would be accepted by the FDA in the USA, and maximum levels that were more than fifty times higher than the FDA limit [21,22]. Reductions in mycotoxin levels are likely to be particularly important to people in developing countries who are more likely to purchase food from lightly-regulated local markets such as the ones studied in China [22]. In a recent meta-analysis, encompassing 21 years of research, Pellegrino et al. [23] conclude that Bt maize is healthier than its close non GE varieties, as no negative effects have been documented and the levels of aflatoxin on produce are lower.

There are some cases where GMO crops can lead to options for consumers that are actually healthier than traditional varieties. As mentioned before, these are "second generation" GMOs. One example is a soybean variety that was engineered to have lower levels of trans-fats [24]. Scientists have also created corn with 169 times more beta-carotene, six times more Vitamin C, and twice as much folate; and cassava with 30 times more beta-carotene and four times more iron [25]. Perhaps the most famous example of genetic engineering for improved nutritional content is Golden Rice, a variety of rice that has been developed to produce beta-carotene. Rice being a main staple in many poor countries, this type of rice could greatly reduce the incidence of Vitamin A deficiency-related illness, such as blindness and infant mortality [4]. The potential for Golden Rice and the regulatory process that has delayed its use will be discussed further below in the section on regulation.

Anti-GMO advocacy campaigns, targeting companies and product lines, often cause them to engage in ingredient-avoidance [26]. This can increase costs to consumers, and in some cases, lead to a less healthful product. For example, in cases where products are enhanced with vitamins or minerals where certified non-GMO alternatives are expensive or not available [26]. Ingredient avoidance can also be the result of complex verification and regulatory environment that surrounds GMOs in the marketplace [17].

Regarding the arguments on the production side, GMO crops generally see a decrease in total pesticide applications as measured by environmental impact quotient, or EIQ [27]. The EIQ is a commonly-used measure of that compares pesticides across multiple attributes in order to generate a single value to reflect overall toxicity [28,29]. Pesticides vary greatly in their toxicity, and health impacts are much better understood by aggregate toxicity measures that reflect those differences, rather than by simply measuring volumes of pesticides applied. First-generation GMOs have also served to shift the types of pesticide used, with the largest change being to increase the relative share of crop area produced using glyphosate. Evidence suggests that the switch from other herbicides to glyphosate has benefits for the health of growers even apart from any overall reduction in total amounts used [28].

There are different ways of evaluating pesticide toxicity. One distinction is between acute toxicity—representing the harm resulting from a single elevated dose—and chronic toxicity, representing the harm resulting from long-term exposure to repeated small doses. From the perspective of pesticide applicators, the individuals more directly affected by these compounds, chronic toxicity is likely the more important of those two measures. Judged by its chronic toxicity to mammals, glyphosate is a relatively safe compound with lower levels of chronic toxicity than 90% of commonly used US herbicides [28]. The same analysis concluded that a reduction in glyphosate use or its discontinuation (as was recently proposed in Europe) would result in higher overall toxicity because it would likely be replaced by herbicides with higher toxicity.

Surveys in China have shown that farmers who adopted Bt cotton reduced their exposure to dangerous pesticides [30,31]. This benefit likely affected millions of individual growers. In South Africa, the adoption of Bt cotton led to lower rates of accidental poisoning by pesticide, largely as a result of reduced requirements for pesticide applications [32]. For similar reasons of reduced requirements for pesticide application, it has been projected that the adoption of Bt rice in China could have significant positive effects on farmer health [33].

4. Farm-Level Impacts

At the farm level, GMO crops have the potential to improve the sustainability of agriculture by reducing herbicide, pesticide, and fertilizer use, by reducing greenhouse gas emissions, by enabling sustainable practices such as no-till production systems, and by increasing yields, thus leading to less need for conversion of natural ecosystems into cropland.

Qaim and Zilberman [34] suggest that first-generation GMOs reduce pest damage and allow plants to reach their potential output in optimal conditions. Yield gains from first-generation GMOs are expected to be significant in areas with high susceptibility to pests. Furthermore, reduced pest damage may provide incentive to additional investment in other inputs, such as fertilizer, leading to further yield gains. This means more food can be grown with existing land resources. Klümper and Qaim [35] completed a meta-analysis of 147 studies on pesticide use, yield, and farmer profits. They found that on average, GM crops increased yield by 21.6%, reduced pesticide quantity by 36.9%, reduced pesticide cost by 39.2%, and increased farmer profits by 68.2%. There is heterogeneity in the results, as apparently some of the early GMO varieties had traits introduced to varieties less appropriate for the location they were planted. However, the effects in general are impressive. The empirical evidence confirms that the farmers who benefitted the most from GMOs were in fact the poorer farmers in developing countries who had fewer options for pest management and who were more vulnerable to outbreaks.

Besides the yield increases, which help support growing populations in developing countries, the main beneficial effect of GMOs in terms of sustainability is probably the decline in pesticide use. We consider the personal health benefits of reduced pesticide use for consumers and farm workers in the health section above. However, pesticides have long been a major environmental concern as well. Rachel Carson's "Silent Spring" [36], a cornerstone in the American environmental movement, dealt mostly with the highly toxic pesticides used in the 1950s. GE technologies allow significant reductions

in pesticide and herbicide use, compared with traditional crops, and lower the environmental impact of agriculture. Two major "first generation" traits can be discussed in this context: insect resistance (IR) resulting from the aforementioned Bt trait, and herbicide tolerance (HT) with respect to the herbicide glyphosate.

A systematic survey of pesticide use on three major GMO crops in the USA—HT soybeans, HT maize, and IR maize—found that, relative to farmers planting conventional varieties, farmers who adopted GMOs reduced the total quantities of pesticides applied in the cases of HT maize and IR maize, but increased total quantities in the case of HT soybeans [27]. Looking at EIQ, the overall effect of GMO on pesticide applications becomes unambiguously positive for the three main crops cultivated in the USA. Farmers who adopted HT soybean and maize used herbicides representing lower total EIQ than those who planted conventional varieties, while those who adopted IR maize used insecticides at a level that also represented a lower EIQ than the levels used on conventional varieties [27,37].

Two concerns regarding HT and IR are resistance build-up for glyphosate and the potential negative effects of Bt toxins on non-pest species. The latter effect seems to be minimal, as the toxins are transferred by ingestion of plant parts and are quite specific to pest families. Bees are unaffected by it [38]. As for the former, resistance to pesticides is not unique to GMOs and there are hundreds of non-GMO examples of herbicide resistance developing in weeds [39]. In the case of glyphosate, despite first being used in the USA market in 1974 and having its use become widespread following the introduction of the first glyphosate-tolerant crops in 1996, glyphosate maintains its effectiveness against most weeds, and 90% of farmers of cotton, maize, and soybean in the USA choose to continue to plant a glyphosate tolerant crop and to use glyphosate [40]. As weed resistance does inevitably increase, however, there are strategies that can be used to maintain effectiveness of HT varieties, even in the presence of resistance. Refuges can be designed with an understanding of population dynamics so as to optimize the balance between resistance build-up and yields [41]. Weed management and selective herbicides can also be part of a strategy to maintain effectiveness of HT [42,43]. Even if resistance leads to the gradual reduction in some of the environmental benefits of first-generation GMO crops, those crops nonetheless show environmental benefits over a significant period of time. The best opportunity in extending these benefits lies in continuing research into new traits [44]. Gene editing using CRISPR, because of its specificity and relative accessibility, provides a particularly promising avenue for extending and expanding benefits that first-generation GMOs have shown in reducing pesticide use.

One more concern, both on the farm and aggregate level, is about the potential loss of crop diversity with GMOs. The reduction of variety scope, which could lead to monoculture, is dangerous for any crop. If all available varieties are similar, they could be more susceptible for a new pest. Moreover, a limited choice of varieties might lower the average efficiency of the crop. To evaluate that concern, Krishna et al. [45] completed repeated surveys with 341 farmers using a four-visit panel design. Their findings showed that despite an initial decline in varietal diversity following the introduction of transgenic varieties, by the end of the study period (in 2008), with 90% adoption of transgenic varieties, the level of varietal diversity had returned to the level it had been prior to adoption. In this case, it was found that the main limiting factor on diversity was simply the number of available transgenic varieties. As gene editing technologies enable cheaper and easier creation of new varieties, the likely impact of genetically engineered crops on agricultural biodiversity will likely decline. It is worthwhile to mention that similar concerns were raised with traditionally bred varieties initially released during the "green revolution" in the 1970s. However, research institutes ended up introducing about 8,000 high yielding varieties to suit most growing conditions [17].

Shiva [46] suggests that one of the dangers of GE in agriculture is that over-reliance on genetic solutions can crowd out other solutions to pests and other challenges in agriculture. A diversity of approaches to agricultural sustainability will almost certainly have more success than a reliance on any one technology. However, this argument is all the more reason for arguing that genetic engineering

should not be overly restricted to the point that it is prevented from making the fullest possible contribution to agricultural sustainability.

5. Aggregate Effects

A vast body of literature, reviewed above, recognizes the positive effects of GMO variety introduction on yields and farmer income. This increase in yields aggregates to a larger supply, which means that the same amount of food and fiber can be grown using less resources such as land, water, and chemicals. However, higher supply can also lower global food prices, increasing demand and to some extent attenuate or even reverse these effects. To study these aggregate effects, the individual yield studies need to be incorporated into a larger framework that integrates supply and demand forces.

To conduct this analysis, one first needs to estimate the impacts of GMOs on aggregate supply. This can be done by simply aggregating estimated benefits in a meta-analysis approach or by statistical estimation of a shift of supply due to GMOs. After estimating the supply effect, analysis needs to integrate supply and demand to assess impacts on prices and welfare. This second stage can be done either by partial analysis that only considers the impact on grain markets, or by general equilibrium analysis that assess the impact throughout the economy.

Brooks and Barfoot [47] use multiple estimates of impacts of GMOs on yield and growing costs at different locations, aggregate them, and assess the impact of GMOs on the farm sector using partial analysis. They estimate the effect of GM technology on global farm income to be $18.8 billion in the year 2012, and $116.6 billion from 1996 to 2012. This represents a 6% increase in the value of global production of maize, canola, soybeans, and cotton.

It is important to distinguish between the impact of GMOs at the intensive and extensive margin. The intensive margin effect occurs when farmers switch from conventional to GMO varieties, thus increasing yields and production due to the modified traits. The extensive margin effect occurs when GMO varieties allow for the expansion of the effective production area, either by the genetic traits themselves (e.g., drought tolerance) or by the economic gains they bring, overcoming costly obstacles that prevented expansion of cropland before. There is a concern that GE crops are contributing to deforestation. Increased soy acreage is blamed for deforestation in Argentina and Brazil [48,49]. However, it is hard to tell the share of GE technology's responsibility in this process, which is driven primarily by growing world demand. The yield effect of GE, rather, is likely to attenuate deforestation caused by increased demand. Evidence suggests that some of the effects that GMO crops have at the extensive margin is in fact the result of double-cropping on plots of land that were already cultivated rather than bringing new land into cultivation [50,51]. GMO crops engineered with herbicide resistance enable planting earlier in the growing season by reducing the need for pre-emergence weed control; this in turn provides the additional time needed to plant a second crop in the same season [52]. To the extent that this is the case, the introduction of GMO crops could have a significant benefit for the agricultural land footprint by greatly increasing annual productivity without expanding the area of land cultivated [53].

Barrows et al. [51] estimate statistically the impact of GMOs on yields and then derive impacts on aggregate supply taking into account the extensive margin effect. They integrate the supply effect with demand estimates and obtain partial equilibrium effects on outputs and prices. They estimate the average effect on prices of soybeans, cotton, and corn to be 33%, 18% and 13% lower than what their respective prices would have been without GM technologies. Much of these gains are due to extensive margin effects, which mostly apply in land already used for agriculture. At the same time, they translate the land savings from current GM penetration rates to GHG emissions savings, finding that GM is responsible for a decrease in emissions comparable to one eighth of all automobile emissions in the US. Other ecosystem service benefits from these land savings are not presented, but surely are positive as well.

Mahaffey et al. [5] use a computable general equilibrium (CGE) approach. In this approach, different market parameters are used as inputs for a computerized model of global agricultural markets and trade, and an equilibrium is computed numerically. Comparing scenarios of global ban on GMOs and increased GMO penetration, they calculate the loss in welfare (profits plus consumer benefits) from a global ban on GMOs. The total welfare loss from a global GMO ban is estimated by Mahaffey et al. to be $9.8 billion yearly. They note that, while the ban is predicted to increase food prices around the world, increases would be sharper in poorer countries, where the average expenditure on food is already higher. India, for example, would see a food price increase of 2.2%. Another interesting finding in this study is about the potential environmental effects of a global GMO ban. The main environmental effect, driven by the lower yields of conventional crops, is the expansion of cultivated area at the expense of forests. This alone results in a 13.8% increase in GHG emissions from agriculture.

The potential savings in land use, as emphasized by Mahaffey et al. [5], is one of the significant contributions of GMOs in terms of sustainability. As GM crops are more productive, they could in theory carry an incentive to transform more natural areas to cultivated fields. However, Mahaffey et al. [5] results predict a lower total land use with GM, probably as the increased yields depress prices enough to prevent the expansion of cultivated land. Yet, GE technology does allow for an extensive margin effect without expanding the total cultivated area, by means of double cropping. Herbicide tolerant traits allow treating crops with herbicide to prevent unwanted weeds from growing with the crop. This means some time-consuming (and carbon-emitting) practices, such as tilling, can be skipped. The result is a longer period of time where fields are available for productive use, allowing double-cropping: growing two crops on the same plot of land in the same year. This practice, in fact doubling the growing area and allowing more food to be grown at a given year, is now common among soy growers in Argentina and Brazil. In fact, up to 70% of cultivated area in Argentina were dedicated to soy in the early 2010s, creating a desire for some diversification by double cropping with maize [53]. Research has shown that double cropping has the potential not only to raise yields but also to reduce yield variability in the Northern Pampa areas, where this practice takes place [54].

6. Distributional Effects and Political Economy Factors

As with many productivity-enhancing technologies, GE technology has the potential to generate positive gains in aggregate. However, any new technology can create winners and losers even while increasing the total surplus. We look at the distributional effects on the micro and macro level. We find this analysis important in terms of sustainability, even though it only marginally touches classic environmental issues. Sustainable agricultural practices, we believe, should benefit all parties involved for its continuity.

On the micro level, many critics of GM technologies claim that it has few or marginal (if positive at all) benefits for farmers, and that most of the gains are kept in the hands of a few corporations based in developed countries. The main "culprit", according to some activists, is the publicly traded company Monsanto, which has made major investments in agricultural biotechnology beginning as early as 1996 [3].

Most economists dealing with GE technology view the subject differently. The NRC [38] survey studies show that the economic gains of GMOs are distributed between farmers, consumers and seed companies. Uptake rates of GM crops—in the US and virtually any other country where they are allowed—are seen by economists as evidence of their evident economic benefits for farmers. As mentioned in the farm-level impact section, Klümper and Qaim [34] find an average increase of 68% in farmer profits as a result of GM crop adoption, while the total production costs are raised by merely 3%. This result is the complex effect of both yield increase and decrease in other costs, especially pesticide costs. Farmers using GM crops enjoy other benefits, which are harder to estimate with dollar figures. For example, lowering yield instability and reduced adverse health effects by noxious pesticides have been observed in China and South Africa [32].

A common claim by GM opponents is that farmer gains are eroded because they are contractually forbidden from sowing seeds from the plants they grow. This is not always true, as national patent laws do not usually hold overseas and local enforcement level varies. For example, Monsanto sued a Canadian farmer growing their patented canola seeds without purchasing them. The company won the case, yet was awarded no compensation [3]. In India, some amount of "piracy" is observed, where GM varieties have been hybridized with local varieties [17]. Yet, to acquire certified GM seeds, one usually needs to purchase them from a legitimate dealer. Again, the fact that some farmers choose to purchase GM seeds year after year suggests that, even when the cost of annual seed purchase is considered, farmers still consider themselves better off with GM crops. Finger et al. [55] find that, while seed costs in GM crops are higher than in conventional ones, the total profitability of GM crops is still mostly higher.

The "must buy seed" claim also fails to acknowledge that many non-GM commercial varieties are first generation hybrids, for which seeds need to be bought from dealers as well. Moreover, sowing self-grown seeds is not a free alternative to buying seed. When the seeds themselves are the marketed products, for example in cereals, sowing self-grown seeds implicitly means buying them at market price. For GM varieties, a theoretical market price (absenting a company exercising some degree of market power) would be the downstream price of the seeds themselves (e.g., corn kernels). Even when the end product is not the seed itself, as with cotton, using self-grown seeds means taking up the extra costs and risks involved in self-storage (preparing seeds for storage, potential loss to pests, water damages, theft, etc.). Purchasing restrictions for GM varieties, while potentially alien to a traditional, autarkic agricultural systems, are neither a new phenomenon nor a major source of loss to farmers.

One clear loser from GM technologies are some chemical companies based in developed countries. Graff and Zilberman [2] argue that European bans of most GM crops cannot be entirely explained by consumer preferences. They make the point that Europe seems more tolerant to research techniques such as cloning and stem cell research, which are controversial in the US. Therefore, "fear of science" is unlikely to be the reason for this policy. They claim that other political factors might be in play. Mainly, they suggest that facing public outcry about pesticide risks in the 1970s, European firms heavily invested in developing safer chemical solutions for pest control and other agricultural inputs, while US firms invested in life science technologies that led to most GM varieties. GM crop adoption lowers the market share of European corporation in the crop protection markets, which dropped from 55% in 1991 to 47% ten years later. A sign of the changing reality is that Bayer, a major European chemical company, is in the process of purchasing Monsanto. The European Commission recently announced the conditional approval of this merger [56].

A transition to an agricultural system with stronger economies of scale could take many farmers out of business, especially in developed countries. This process has been in place even with an effective GM ban: the average farm size in France and Germany has increased by 31% and 32% respectively over the first decade of the 21st century (data from agricultural censuses in Eurostat [57,58]), although the average farm size in the USA is still three times larger [59]. It has been suggested that GM crops are seen as a proxy to this transition or as factors which would accelerate it, raising opposition from smaller farmers with great political power [2].

On the macro level, it would seem like the potential gains from GM technologies are far greater in developing countries than in the developed world. The yield effects seem much higher in developing countries [34,52], while lower food prices benefit the poor, for whom food costs constitute a relatively larger share of the daily budget [60]. Mahaffey et al. [5], estimating the cost of a global ban on GMOs, surprisingly find that the largest winners of such ban would end up being two major GMO growers: the USA and Brazil. Other GMO exporting regions, such as Canada and South America, also see positive gains from a GMO ban. The authors explain this result by noting that major GMO growers are also major exporters. With a ban on GMOs, world prices increase. As the exporting countries are likely to make most of their gains from producing, the increased consumer price only slightly attenuates their gains due to profit increases, as export prices rise. On the other hand, major importers, such as

China, the Middle East and North Africa, India, and Europe, see negative gains from a GMO ban: they are not large exporters of food, so rising export prices are irrelevant for their profits; yet they are food importers, hit by increased prices for food, animal feed, and fiber.

7. Environmental Effect, Biodiversity and Sustainable Development

Given the relatively inelastic demand for food, the positive effect that GE technologies have on yield are associated with a reduced agricultural footprint in terms of the use of land, energy, water, and chemical inputs. Having discussed the effect of GMOs on reducing pesticide use earlier, we focus here on the effects on land use and carbon emissions. Barrows et al. [51] estimate for the year 2010 that maintaining similar output for corn, soy, and cotton without GE crops would have required at least an additional 13 million hectares of cropland. Other research suggests that a global ban on GMOs would increase total cropland by 3.1 million hectares with 0.6 million coming from deforestation [5]. That can be compared to an opposing scenario where GMO adoption worldwide is brought to a level equivalent to the level in the USA: under that scenario, global cropland area actually declines by 0.8 million hectares [5].

Reducing the land footprint of agriculture—particularly that part of the footprint that comes at the expense of tropical forests—has a large impact on greenhouse gas emissions. Taking the three estimates above—ranging from 3.1 million to 20 million hectares of additional cropland that would result from eliminating GM crops—and coupling them with a common estimate of greenhouse gas emissions from land cover change of 351 metric tons per hectare of converted land [61]—we can conclude that GMOs have averted emissions equivalent to between 1.1 Gt and 7.0 Gt of carbon dioxide. Those estimates are equivalent to 19–135% of one year's emissions of the USA—which were 5.17 Gt in 2016 [62]—although this is an estimate of a one-time conversion rather than an annual value.

In addition to reducing emissions from land cover change, GE technology can positively affect other components of agricultural emissions, particularly by reducing energy and fossil fuel use and by enabling reduced tillage and no-tillage agricultural practices. Traditionally, tillage and herbicides are used to prevent unwanted weeds growing in the field. Herbicides are toxic to most plants, and must be applied in absence of the crop. Herbicide resistant crops allow for herbicide application at the presence of the crop. Herbicide eliminates the weeds, and the GM crop is left unharmed. Prior to the introduction of herbicide resistant varieties of canola, the primary herbicides used for the crop required tillage for their effectiveness [43]. Following the introduction of herbicide resistant canola varieties, from 1995 to 2006, herbicide application rates on canola in western Canada decreased by 53% while the percentage of farmers using zero- or low-tillage rose to 64% [43]. Similar patterns were observed in the USA where between 1995 and 2009, the area of soy under no-till management increased by 65%, with most growers stating in a survey that herbicide tolerant soy was the most important reason for their shift to no-till practices [13,37]. As a result of the shift to no-till practices in soy production in the USA, fuel consumption per acre decreased by 11.8% and total greenhouse gas emissions declined by 4.8 Mt. Globally, the shift to no-till practices that resulted from the adoption of herbicide tolerant crops is estimated to have led to the sequestration of soil carbon equivalent to 17.6 Mt of carbon dioxide.

In the farm-impact section, we discussed the potential problem with monoculture. In terms of agricultural biodiversity in general, genetic engineering in fact offers pathways for the preservation of heirloom varieties that might be otherwise lost and for the maintenance of crop biodiversity more broadly [52]. The decreasing costs of inserting a trait into a crop variety—a trend accelerated by the introduction of technologies such as CRISPR-GE—will not necessarily reduce diversity in crop varieties. Experience with soy has in fact shown that much of varietal diversity has been maintained [63]. In some cases, genetic engineering may be able to conserve agricultural diversity that would otherwise be lost, for example by providing pest resistance to varieties that would have otherwise been abandoned because of levels of pest damage [52].

One of the most advanced and most promising examples of the use of genetic engineering to assist in species rehabilitation is that of the American chestnut. After the introduction of the fungus

Cryphonectria parasitica in 1876, American chestnuts were decimated in their home range with the loss of an estimated three billion trees [64]. To date, the continued presence of the fungus in the landscape has prevented American chestnuts from re-colonizing their home range of eastern North America—an area where they were once perhaps the most dominant and ecologically-important tree species. In recent years, a team of researchers has developed a transgenic variety of the American chestnut with an introduced wheat gene that allows the tree to produce an enzyme that breaks down the harmful oxalic acid produced by the *C. parasitica* fungus [64]. Field trials suggest that this tree may resist the fungus as effectively as do species of Asian chestnut that evolved alongside the fungus. Further research is needed and regulatory hurdles remain, but this work raises the possibility of the American chestnut eventually being re-established in its home range. Work on the American Elm—similarly wiped out of its range in eastern North America by an introduced fungal pathogen—provides another example of the potential role of genetic research in species recovery efforts [65].

GE could be a powerful tool for biodiversity conservation more broadly. Projections have been made that by 2050, 15–40% of living species could be committed to extinction, primarily as a result of habitat loss and changing conditions under climate change [66]. The change in climate predicted to 2100 would require rates of species adaptation that are 10,000 times higher than adaptation rates typically observed in nature when species are observed to adapt to new conditions [67]. Assisted adaptation may be one of the most viable options remaining to enable the survival of certain species under a changing climate [68]. Scientists may be able to deliberately introduce genes into wild populations that would assist species in their adaptation to changing conditions. Of course, these kinds of deliberate interventions are not to be taken lightly. Proper research and regulation would be necessary for such interventions. Yet, in some cases, such as a small endangered population susceptible to a new pathogen, genetic technologies could in theory save species from extinction.

One additional environmental concern regarding GMOs is the potential drift of introduced traits to wild populations. This could happen by cross pollination of GE crops with wild relatives, or by mechanisms of horizontal gene transfer (HGT). The former is quite unlikely in most cases, as commercially grown crops are usually genetically distant from their wild neighbors, but has been shown to happen. Some current regulation and practices aim to lower the incidence rate of these events [38]. The latter seems to be very rare among eukaryotes, and Keese [69] describes HGT as presenting "negligible risks to human health or the environment". In fact, the revolutionary aspect of GE is indeed overcoming the extreme difficulty of HGT to increase the potential pool of traits available in crops. The main question is, what are the potential threats from such a scenario? Anti-resistance build-up practices can address multiple drift problems that may arise from agricultural practices. When it comes to impacts on wildlife, the current insect resistance trait, coding for Bt toxins, has been shown to only hurt specific families of pests. Areas where Bt crops are grown do not show a decrease in the number of insects and arthropods in general, in spite of significant Bt plants presence [38]. Future GE traits need to be evaluated for such potential outcomes, yet the current experience does not show significant ecological damages from GMOs.

8. Intellectual Property

Private companies have property rights on some biological innovations, including crop varieties and traits that are offered to farmers. Even though large seed companies, selling unique hybrid seeds, have existed since the 1930s, intellectual property rights on biological innovations were only recognized in the USA in 1980 and then started spreading globally through international trade agreements [70]. Is this modern practice of agricultural innovation a sustainable one?

Available GM varieties are the product of a long research and innovation process. Innovation involves the creation of basic knowledge on genetics and the technologies for genetic manipulation, continuing with the discovery of various genes and their phenotypical expressions, integrating the agronomic understanding of the challenges plants face in the field and potential mechanisms to deal with them, successful application of one or multiple genes to deal with this challenge, field

testing, compliance with safety regulations, and adoption by farmers [71]. The costs of this process are shared between governments and the private sector, where governments mostly fund basic research, and private sector companies deal with the application and commercialization. This is sometimes referred to as the "educational–industrial complex" [72].

The need to assert these property rights comes from the heavy investment required to create new varieties. The innovation is not the seed itself, but a new genetic trait or traits that add to its value to the farmer. Unlike hybrid seeds, which grow to be useful plants but have less efficient descendants, GM traits are largely hereditary. Thus, GM innovations can essentially be copied for free by planting the seeds produced. Property rights are therefore essential for cost recovery of the innovation process, as well as proper profits to motivate further innovations [52].

Private sector investment in agricultural R&D has been increasing faster than public investment for the past three decades and became a majority in OECD countries in the year 2000. At the same time, R&D investments in seed and biotechnology surpassed the traditional R&D investments in machinery and chemical products [70]. These increased investments have led to a greater variety of GM crops available at present, and likely would not have happened without the assertions of property rights on GM traits. At the same time, GM seeds cost more than conventional ones, increasing farmers' expenditures but overall increasing profitability as well [34].

A few concerns regarding intellectual property rights and GMOs can be addressed by proper regulation. Mainly, the concern is that property rights limit the potential scope and implementation of new GM variety development. Introducing a new GM variety can require the licensing of up to 40 patents and licenses, making the process very expensive and bureaucratically hard for smaller companies [52]. A related problem stems from the nature of the property right itself. Some rights include terms for non-excludability, meaning that anyone can use the technology while guaranteeing royalty payments from marketed products developed with it. Others, such as the essential technology of using agrobacterium to transfer genes to plants, are held exclusively by companies like Monsanto. This limits the availability of potential innovations, resulting in "orphan" crops which see less investment, a condition that might specifically hurt developing countries [70,73]. Thus, setting proper property rights mechanisms for development technology, balancing firms' incentive to create these innovations while ensuring the broad use for research, is important for increasing the spread of GM crops: in particular, a mechanism such as a clearing house that would allow free and low-cost access to intellectual property for the development of varieties that serve the poor or orphan crops [2]. Indeed, some institutions, such as the Public Intellectual Property Resource for Agriculture (PIPRA) or African Technology Foundation (ATF) aim to serve this purpose. However, the main constraints for the introduction of biotechnology are regulations.

9. Labelling and Consumer Choice

The discussion of labelling is essential for the sustainability debate, as labelling and consumer choice end up determining a product's market penetration. Thus labelling policies can promote—or handicap—the gains of GE in terms of sustainability. The scientific consensus is that food consisting partly or entirely of GM crops is at least as safe as food consisting of conventional crops [17]. However, there seems to be a significant consumer desire to know if food products contain GM components. This has led to various food products to be labeled "GMO-free", and the commonly used and regulated "USDA organic" label also ensures the lack of GM components in a product. Some people find these voluntary labels insufficient, and demand mandatory labeling of food products containing GMOs. However, economists are concerned about labels which play on misguided beliefs and information gaps among consumers, as they might distort purchasing choices from products that are better for general welfare and the environment. The share of more sustainable agricultural practices, using GM crops, could be higher if not for these distortions. The issue of GMO labels is hotly debated, and different regulatory approaches exist for it.

In the EU, labeling of products containing above a miniscule amount of GMO "traces" are subject to special labeling [74]. This type of regulation often crates absurdities. For example, refined products such as sugar have no trace of GM protein or DNA. Thus, conventional refined sugar and refined sugar from GM sugar beet are chemically identical [75]. Sugar products derived from GM sugar cane has been authorized for sale in the EU based on a risk assessment panel [76]. Yet, they require a mandatory GM label, even though they pose no additional risks to regular sugar. A consumer mostly concerned about potential negative health effects from GMO consumption might still avoid the product, forgoing economic and environmental benefits. On the other hand, "raw" GM corn (including GM protein and DNA) is in fact used for animal feed in the EU, yet meat and dairy products from GM fed animals do not require labeling as the meat and dairy do not contain "traces" of GMOs, certainly not above the mandated threshold level [77].

In the US, voluntary labeling is the norm. California, the leading US state in organic production, has seen two legislative initiatives for mandatory GMO labeling in recent years, both rejected by a narrow margin. Proposition 37, a state-wide ballot measure (referendum) proposing such labeling on food products sold in California, was rejected by a majority of 51.4% of voters in 2012. Zilberman et al. [78] state that once the discourse started including the option for voluntary labelling, and once the estimated consumer costs of the labelling were published, support for the proposition shrunk from about 60% to the minority it had on the ballot. Organic growers were the major financial supporters of the mandatory labelling campaign, which also enjoyed more volunteers. Biotech companies, as well as retails chains, were against it. Two years later, a similar parliamentary measure (Senate Bill 1381) was rejected by a small majority in the California Senate.

Supporters of these initiatives claimed that consumers have a right to know the ingredients of purchased food. Some economists, while supporting this claim, think that voluntary labels are sufficient for allowing informed consumer choice, and that mandatory labeling would be inefficient and unfair. The main issue is that wrong perceptions of GM foods make labeling misleading, and that mandatory labels exacerbate this phenomenon. Mandatory labels perpetuate debunked beliefs regarding GMOs, and limit their potential benefits both in human welfare and in environmental benefits.

Scientific evidence seems to suggest that people have negative misperceptions about GMOs, and that these misperceptions play a role in their food choices [79]. Mandatory labeling thus pushes consumers to make less than optimal choices. Moreover, government mandated GMO "warnings", without proper and objective informing of the public on the potential benefits from GMOs, perpetuates these misconceptions and might actually be misleading.

Zilberman [80] argues that mandatory labeling is an appropriate policy when a food ingredient might be unhealthy or dangerous in large amounts, such as alcohol. As evidence points that GM crops are at least as healthy than conventional ones, he argues that non-GMO food preferences are equivalent to other non-health related preferences such as eating only kosher or halal food, buying "fair trade" products, etc. In these cases, most people would seem to agree that mandatory labeling should not be the norm. Moreover, he argues that many people are misinformed about the safety of GM food and its potential social and environmental benefits, making the warning style labeling of GM foods even more inefficient by reducing the share of GM foods that would have been bought with complete information.

Consumer misinformation is taken seriously in countries such as Belgium and Sweden, where regulations do not allow for "negative labels" (such as "free of X"), except for potential allergens such as nuts or gluten. This regulation, taking into account that negative labels are frequently irrelevant and misleading to the average consumer, also prohibit "GMO free" labels in these countries [77].

The concerns of Belgian and Swedish regulators are backed by empirical findings. Perception and information seem indeed to play an important role in consumer choice, and the framing and labeling of foods are crucial. The plethora of ever-evolving food packaging and commercials are evidence that food producers are aware of this fact. Heiman and Zilberman [81] show how negative framing creates stronger resistance to biotechnology. Huffman and McCluskey [82] survey studies showing that

customers have a higher willingness to pay for second-generation GMOs, where traits are designed to enhance the nutritional value of food, but this sometimes comes with some conditions such as the added trait coming from the same species. McFadden and Huffman [83] show that when people are fully informed, they are in fact willing to pay more for potato products labeled "biotech" when the chemical composition of the potato has been designed to have lower rates of toxic Acrylamide formation when baked or fried. In the real world, however, complete information is not the rule. Labeling regulations thus need to acknowledge this fact and its consequences for the environment.

10. Regulation

Regulation of research and implementation of GE varieties are debated around the world. Some people fear the unintended risks of GMOs, pushing for more restrictive policies. DeFrancesco [19] poses the question "How safe does transgenic food need to be?" in her article of the same title. In it, she highlights the tension between the necessity of regulations to reduce the risk of harm and the concern that overly stringent regulations will prevent society from benefiting from advantageous developments in agriculture. Striking this balance between risk and benefit is fundamentally a social decision rather than a scientific one. However, we believe that the available science suggests that decisions surrounding GMOs to date have erred too far in the direction of risk avoidance, particularly given the lack to date—after more than 20 years of commercial production—of concrete harm that is directly attributable to GMOs.

Opponents of GMOs have frequently invoked the precautionary principle (PP) to advocate for limitations or bans on GMOs. The PP asserts that, when a new technology is being considered, the onus should be on the proponents of the technology to prove the absence of any risk of harm from the technology rather than the onus being on opponents of the technology to prove the presence of a risk of harm. However, it is impossible to prove a negative—i.e., to conclusively prove the absolute absence of risk—meaning that, in its strongest form, the PP effectively stifles any new innovation [1].

These questions of the regulation of genetic engineering have been given new life by the introduction of new gene editing technologies such as CRISPR and related technologies. These technologies make possible the editing of plant genomes with more precision than before. In many cases, they are also able to modify genomes without introducing transgenes, thus resulting in a plant that is not distinguishable from a plant that was developed using conventional breeding techniques. This blurs the boundaries surrounding what counts as a GMO and poses novel questions for regulators and for public acceptance. As these boundaries become blurred, thresholds for regulations can potentially be drawn at differing points along a spectrum of techniques [15]. At present, this spectrum of potential regulatory approaches can be seen in differences between those countries that have taken a process-based approach to regulation that renders any products produced by gene editing techniques potentially subject to regulations. These jurisdictions include the EU, Australia, and New Zealand. The more permissive regulatory regimes are those that take a product-based approach–this is the approach that has been taken by Argentina, Canada, and the USA. Using a product-based approach potentially excludes many gene edited products from being subject to regulation [15,84].

A reasonable strategy in the regulation of new technologies is to begin stringently and then become more permissive as experience allows. This is the approach advocated by Araki and Ishii [15] regarding newly emergent CRISPR technologies. However, there is a risk of regulatory frameworks becoming ossified at a particular level of rigor. This seems to have partly been the case with more traditional GMO varieties that, unlike CRISPR, have already been in the human food chain for more than two decades. Any regulatory framework must balance the risk of harm against the costs of delay. With an emerging technology when the risks are less known, it is reasonable that the balance would be tilted towards more stringent regulations. However, over time, knowledge of potential risks—or relative lack thereof—increases while the cost of delayed benefits mounts. As those twin processes occur, the balance may shift such that a more permissive regulatory framework is more socially-beneficial.

An excellent example of regulatory delay imposing large costs that may not be justified by improved public safety is that of Golden Rice. Golden Rice is a rice variety that can synthesize beta-carotene, thus providing a potential avenue to address Vitamin A deficiency via an abundant staple food. Despite having been available for commercialization since 2002, Golden Rice has not yet been approved for commercialization in any country (although the Philippines in 2017 began the approval process). A 10-year delay in the approval of Golden Rice may have resulted in millions of people losing their eyesight as a result of Vitamin A deficiency [85]. Converted into monetary terms, and considered together with GM corn, rice, and wheat, the potential benefits that are foregone for each year of delay is between \$27 and \$82 billion. Similarly, Wesseler et al. [4] consider a subset of forgone benefits due to delays in GM variety approval in African countries, including regular economic benefits of more efficient production as well as the cost of stunting due to malnutrition. The 10 year costs range between \$16.7 and \$479 million for different crops in different countries. These values are the baseline against which the argument of precaution must be measured: given that we will never have perfect information, is the value of the information gained during the course of that one year of delay worth a comparable amount?

11. Conclusions

Agricultural biotechnology provides a set of tools that increases capabilities of agriculture to adapt to climate change and to lower its environmental footprint. It is not a silver bullet, but rather part of a portfolio of approaches to sustainability. Agricultural biotechnology increases the precision and speed of plant breeding, and can expand the genetic material available to farmers. GE consists of several tools that may result in many applications, and each of these applications needs to be evaluated independently. However, regulations should be efficient and balance benefits and risks.

We are at the early stages of application of GE, and applications in agriculture have been heavily regulated. Yet, we have already seen that this technology increases yields, consumer welfare and farmers' income, and reduces emissions and the environmental costs of agriculture. Moreover, GE has the potential to increase crop biodiversity and may play a role in bringing back dormant or nearly extinct varieties or species. Inherently, the knowledge behind GE is a public good. Intellectual property regulations may serve to enhance investment in the technology, but at the same time constrain access to its applications. We review mechanisms to expand access to these biotechnologies, especially for developing varieties benefiting the poor.

The main constraints for adoption of GE technology are actually regulatory. Existing regulations that practically ban utilization of the technology with certain crops in different parts of the world have been found to hurt the poor. Regulations should be designed to balance risks and benefits, as excessive precaution delays the valuable benefits of the technology. Consumers and farmers should be further educated about the properties and merits of GE technology.

GE is in its infancy. It enhances human capability to deal with challenges posed by climate change, food security and environmental protection. It will be a major mistake to abandon GE technologies or heavily restrict their progress because of perceived risks. Instead, society should nurture these technologies and carefully evaluate and utilize them to the benefit of humanity and the environment.

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