**INSIDE THE MINDS**

# Trends in Agriculture: GMOs and Organics

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# Challenges and Opportunities Facing the Evolving Field of Genetically Modified Organisms (GMO)

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Chris Holly's PhD work—conducted at Mississippi State University and funded by the United States Department of Agriculture—focused upon microbial and plant community dynamics in agricultural systems. After graduating from Mississippi State, Dr. Holly earned his JD, magna cum laude, from University of Mississippi School of Law. Now, as the senior associate in Cooley's Agricultural Biotechnology practice group, Dr. Holly's practice involves helping clients navigate the legal waters surrounding the most cutting-edge technology in this field.

**Introduction**

The field of genetic engineering has revolutionized the agricultural industry over the past few decades. This revolution has led to the development of, *inter alia*, pesticide resistant crop species, which by their very nature have dramatically altered farming practices the world over. These changes, not only to the genomes of the world's commercially important crop species, but to the very way in which we as a people interact with the land, have thrust this highly technical branch of biology into the forefront of the national psyche.

Now, with the advent of the next generation of genetic engineering techniques and the explosion of research in this field, the very definition of what is considered a genetically modified organism is being intensely debated. As the lines of what constitute a genetically modified organism become less clear than in years past, many in the scientific community prefer simply to refer to plants improved through the use of modern biotechnology.

The evolution occurring within the definitional bounds of what constitutes a genetically modified organism is being mirrored in the dynamic nature of the public's perception of these organisms and their place in society. The role of genetic engineering will only become more important in the coming years, as a result of the world's ever increasing population and the concomitant demand for food. As practitioners in the field, we will be tasked with staying abreast of the scientific, legal, and public policy considerations surrounding this landscape, to help clients navigate the legal waters of a truly paradigm shifting technology.

**Defining GMOs**

At the most basic level, a genetically modified organism (GMO) is any organism whose genetic material has been altered using genetic engineering techniques. That is, any organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.

Our backgrounds are largely in the agricultural and horticultural sectors. Consequently, when contemplating GMOs, it is mostly in the context of plants. The utilization of a genetic engineering technique, or process of modern biotechnology, to alter a plant's genome is in contrast to what are considered more classical methodologies for bringing about genetic change in a plant—for example, *via* traditional plant breeding. Consequently, a GM plant can also be defined in the negative, as an organism whose genome has in some way been altered *via* a process that is not a traditional plant breeding technique, and thus seen as somehow "unnatural."

For historical perspective, it is important to note that just prior to the advent of what we now view as modern genetic engineering, traditional plant breeding included the use of a variety of historically non-traditional plant breeding processes, such as protoplast fusion, bridging crosses, and chemical/radiation mutation breeding. Furthermore, the plant types we now recognize as representative of well-known crops, such as corn, soybeans, and tomatoes, look very little like the wild species from which these crops were derived by traditional plant breeding. Thus, there is not a bright-line demarcation between what was considered traditional plant breeding and what is now termed genetic engineering.

Already, one can see the nuances of these definitions, as it is hard to clearly define what a "genetic engineering technique" would entail, as even traditional plant breeding can be said to engineer a plant's genome *via* choosing parental lines to cross or by using historically important breeding techniques such as mutation breeding. Further, what actually constitutes "modern biotechnology"? And how does one go about scientifically defining what falls within or outside of a "traditional plant breeding technique"?

It is only through an in-depth discussion of these various parameters that we can develop a common language to discuss what plants may or may not be considered as GMOs.

*Advances: Changing the Definition*

The definition of what constitutes a GMO is constantly evolving, and this is a direct result of the extremely rapid advances being made in the technology. For instance, if you were to have asked what constituted a GM plant back in the mid-'80s, then our answer would certainly have centered on what we would now call a "transgenic" plant. For example, early work creating plants resistant to antibiotics, which was a breakthrough for selectable markers for plant transformation, did so by incorporating chimeric bacterial genes conferring antibiotic resistance into an *Agrobacterium tumefaciens* Ti region, which subsequently inserted the bacterial antibiotic resistance gene into the plant.

This inserted bacterial DNA was heterologous to the recipient plant species. Further, the DNA inserted into the Eukaryotic plant was from an entirely different biological Kingdom, a Prokaryote! As a result of this somewhat recent technological history, a "transgenic" generally refers to an organism that contains a gene not found in the natural germplasm of that organism.

Subsequent to these early transgenic plants, we began to see the advent of plants modified to contain other bacterial genes. The most famous of these early advances were the Bt crops, which are plant species that have been modified to contain and express a *Bacillus thuringiensis* gene. Upon sporulation, many *B. thuringiensis* strains naturally produce crystals of proteinaceous insecticidal δ-endotoxins (i.e., crystal proteins or Cry proteins) that are encoded by *cry* genes. The Cry proteins are generally very specific and have been used as liquid sprays by farmers to control pests since the 1920s.

Thus, with the advent of modern biotechnology, it was only a matter of time before scientists developed ways to express these bacterial genes in plant species, such that the plants would express the Cry protein themselves. These cry genes have now been successfully integrated into several commercially important crop species, including tobacco, corn, and cotton.

As with the very early transgenic plants that were resistant to antibiotics, the Bt plants are also a classic example of a transgenic plant species.

Soon after the development of Bt-transformed crop species, the world witnessed the development of plant species that had been genetically engineered to be resistant to herbicides. One of the most famous, of course, is the glyphosate resistant plants. These plants were genetically engineered to express a bacterial 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme, which was resistant to glyphosate. The EPSPS enzyme is essential for plants to synthesize aromatic amino acids, but glyphosate interferes with the enzyme's ability to participate in the synthesis. Scientists discovered an *Agrobacterium* species with a version of EPSPS that was resistant to interference by glyphosate. By using a particle acceleration method of plant transformation, scientists were first able to put the bacterial glyphosate resistant gene into soybeans. Not long thereafter, other crop species such as corn and cotton were also made resistant to glyphosate, thus enabling the direct application of the herbicide to the plant without deleterious effects to the plant.

Golden rice was developed to produce vitamin A in its endosperm in an effort to provide more of this important vitamin to children living in areas with a shortage of dietary vitamin A. Golden rice was created by transforming rice plants with two biosynthesis genes for production of beta-carotene, a precursor of vitamin A. One of the genes was from daffodil and the other from a soil bacterium.

As you can see, these early GM plants all utilized heterologous, mostly bacterial, genes inserted into the plant's genome and resulting in a transgenic plant species. However, this classic paradigm of what constitutes a GM plant is being radically challenged by new technologies and new methods of genetic engineering that do not result in heterologous genes being introduced into a plant's genome.

*Reevaluating the Definition*

As indicated above, one can see that the evolution of biotechnology has quite literally led to a much-needed reevaluation of our concept of what constitutes a GMO, and in particular, a genetically modified plant.

One of the new plant genetic engineering techniques, which strongly challenge the old concept of what constitutes a GM plant, involves the introduction of endogenous native genes into a plant species of interest.

This new methodology utilizes *A. tumefaciens* mediated transformation that does not result in the incorporation of any bacterial transfer DNA into the plant. Rather, the process makes use of plant nucleotide sequences that mimic the function of bacterial transfer DNA. Plant species can be developed through this process to incorporate desired native traits that may be found in closely related wild plant varieties, but that have been lost in commercial varieties. While there is no universally accepted definition of what constitutes a "native trait," the term generally refers to traits encoded by genes from the natural germplasm pool of a particular organism. So, a question arises as to whether or not the transference of a native gene to a plant within the same genus or species should even be technically considered a GMO as it is currently defined, particularly given the (sometimes negative) baggage that the term tends to have.

Consequently, modern biotechnology and current genetic engineering techniques can now accomplish, at least theoretically, the same thing as traditional plant breeding in much less time and with greater precision. That is, modern genetic engineering can be used to introduce desirable native traits into a plant species, with no resulting heterologous bacterial (or other transgene) sequences being incorporated. The result of these new processes—a plant variety with a native trait of interest—could be derived *via* traditional plant breeding. However, the speed at which modern biotechnology can achieve the same result is orders of magnitude faster and more predictable. This is because traditional plant breeding relies upon altering the plant's genome indirectly, by selecting plants with specific traits.

In a traditional breeding program, a breeder selects desirable parental plant lines to cross, but the changes occurring at the genetic level are unpredictable.

That is, the parental plant's DNA recombines randomly. Conversely, modern genetic engineering can directly manipulate the plant's DNA, thus enabling targeted transfer of native genes that can result in the production of new plant varieties possessing desirable native traits and no heterologous DNA. This allows rapid improvements to already economically valuable and commercially successful plant varieties without unwanted and somewhat uncontrollable genetic changes, as could be the result of doing the same thing using traditional plant breeding methodologies.

**GMOs: Pro and Con**

There are numerous benefits set forth by proponents of GM crops. First, the world's population is presently about 7.4 billion people and is expected to reach between 8.3 and 10.9 billion by 2050. To feed these additional inhabitants, the world's farmers will either need access to more arable land, which is increasingly impossible, or the yields expected from currently planted acreage will need to dramatically increase. The prospect of GM crops offering increased yield potential for important food crops on a per acre basis is one way to address the world's increased demand for food.

Second, GM crops—such as Bt corn and cotton—offer the potential to decrease synthetic chemical pesticide utilization and lower the environmental impact associated with such use.

Third, genetic engineering offers the potential to insert desirable traits into existing crop species that will make these species more tolerant of rising global temperature. For example, genetic engineering could be harnessed to make crop species more resistant to draught or to more efficiently utilize water, which could safeguard global food supplies in the face of global temperature increases.

Fourth, GM crops offer the possibility to create plants with greater concentrations or higher quality of certain desirable plant products, such as nutrients, specialty starches, oils, etc.

Thus, GM crops hold the promise of promoting more environmentally friendly farming practices by increasing crop yields with fewer system inputs, improving resistance to insects, and introducing desirable traits that can help stabilize world food supplies in the face of rising global temperatures.

One challenge faced by GMOs is the continuum of what constitutes a GMO or GM plant, and the public's perceptions of each new iteration. As we have discussed, a genetically engineered plant no longer must simply mean a transgenic plant species that has had a heterologous (i.e., non-native) gene inserted into its genome. Rather, modern biotechnology and new gene editing techniques make it possible to now incorporate entirely native and desirable genes into a target genome with a high degree of precision.

Further, modern gene editing techniques make it possible to merely alter single nucleotides that could silence undesirable or inefficient genes from being expressed in a plant species, some of which are the inadvertent result of traditional plant breeding, and some of which have been evolutionarily conserved but are no longer beneficial today. These new techniques are challenging the old and antiquated notion of what constitutes a GM plant species. Understandably, the general public has some difficulty with comprehending the technical nuances and figuring out how they might impact their real-world implications in agriculture and the food chain.

Opponents of GM crops advance a number of arguments against GMOs, including that they have negative effects on human health and the environment, and, that widespread usage of GM crops will lead to the creation of "super bugs" and weeds resistant to pesticides and herbicides, respectively. They assert that foods produced using GM crops should be labeled as such, and, want researchers and government regulators to give greater consideration to the possible problems of using GM crops.

There are also challenges associated with the promise that GM plant species can lead to increased global food supplies to feed an ever-increasing global population. This challenge is buttressed by the fact that much of the GM crop acreage currently planted does not, in fact, find its way into direct human consumption, but rather is grown and utilized for other purposes. Thus, this is not so much a problem with GM crops *per se*, but rather is a problem with how current crop acreage is apportioned and utilized. For example, some take issue with GM corn being used as a feedstock for ethanol production where other fuel sources not involving the use of agricultural land offer viable alternatives.

**Working with GMOs**

The most frequently genetically engineered crop species are the big three of cotton, corn, and soybeans. While there are plenty of examples of genetically engineered horticultural crops too, they have had somewhat less acceptance in the marketplace as they are normally consumed directly, rather than being fed to animals or processed into manufactured food products. The USDA does a terrific job of tracking the total acreage of GM crops that are planted each year by farmers, and they have been maintaining this database since the mid-1990s.

Cotton, corn, and soybeans are each often genetically engineered to be resistant to one or more herbicides (herbicide-tolerant, HT), as discussed above, with respect to glyphosate. For cotton and corn, the current acreage of HT plantings is approximately 89 percent in 2015. For soybeans, the current 2015 figure is that 94 percent of total US soybean acreage is HT soybean.

As previously discussed, corn and cotton crops containing Bt genes have been available since 1996. Current Bt corn acreage planted in the United States stands at 81 percent in 2015. Plantings of Bt cotton show a similar trend, with 84 percent of the total cotton acreage planted in the United States being Bt cotton.

The ability to “stack” genetically engineered traits (i.e., include at least two genetically engineered traits in the same plant), such as herbicide tolerance and Bt genes, is also very popular. Stacked cotton acreage planted in the United States was 79 percent of cotton plantings in 2015. Stacked corn acreage planted in the US was 77 percent of corn plantings in 2015.

Thus, when considering total adoption of genetically engineered crops in the United States, whether those crops are HT only, Bt only, or stacked crops (i.e., containing HT and Bt), the total acreage of genetically engineered crops planted in the United States in 2015 was 94 percent of cotton acreage, 92 percent of corn acreage, and 94 percent of soybean acreage (remember soybeans only have HT varieties and not Bt varieties).

The most common method of genetically engineering plant species is by *A. tumefaciens* directed plant transformation. As aforementioned, the traditional process utilizes the ability of *A. tumefaciens* transfer DNA to incorporate a gene of interest into a plant's genome.

However, there are a myriad of new genome editing techniques that are being implemented in modern plant genetic engineering, such as zinc finger nucleases (ZFNs), meganucleases, transcription activator-like effector nucleases (TALENs), and the CRISPR/Cas9 system, among others. This branch of genetic engineering involves inserting, replacing, or deleting nucleic acids using engineered nuclease enzymes, which act like scissors to precisely cut a target genome at a desired location. Once the target genome is "cut open" *via* the molecular scissors, then a donor sequence or desired gene can be inserted into the target genome *via* homologous recombination. Alternatively, these systems can be utilized to merely remove genes of interest or delete only certain nucleotides, rather than serving to introduce new genetic elements. These new methodologies are leading to rapid advances in plant genetic engineering, including allowing high throughput methods to be applied to plant transformation.

**Conclusion**

To stay abreast in this field, one needs to do a lot of "leisure" reading in the relevant scientific journals and also in the industry and legal publications. Keeping cognizant of advances in other, seemingly unrelated technologies also helps attorneys to anticipate new trends so that they can guide clients to think out of the box about emerging opportunities and challenges. For example, we quickly realized the potential importance of the advances in drone technology to agriculture and were engaged with our clients from the earliest stages on its implications to precision agriculture.

This sort of both focused and broader reading provides a continually updated backdrop, by which today's events can be placed into context. Further, getting out on the road and talking to your clients in the industry is absolutely invaluable. We often find that an on-site client visit, and its attendant in-depth discussions with the company's scientists, is the most valuable source of knowledge and understanding that is available to attorneys in our field. We invest in having our scientifically trained attorneys spend time in our clients' labs and fields. Regular on-site client visits foster deeper relationships between the attorney and individual client and provides an intimate understanding of the field, as seen from the client's perspective.

Working within a diverse and multi-disciplined team helps lead to better, more comprehensive and increased client representations for cutting-edge technologies such as those involving GMOs. Relevant teams may include attorneys versed in a variety of legal areas such as patents and patent-like protections (i.e., plant breeders' rights/plant variety protection certificates), trademarks, advertising law, food regulatory law, import/export law, transactions/agreements, and antitrust. The legal needs of such emerging technologies often involve the intersection of one or more of these or other legal expertise. Being a member of such interdisciplinary legal teams working closely with your clients can add excitement, additional opportunities to keep abreast of scientific and production advances, and provide feelings of fulfillment in achieving successful legal outcomes in complex, intersecting, and interesting technological spaces.

The best advice is to be passionate about what you do. A solid education and/or work experience in one or more of the relevant scientific disciplines is very helpful in understanding the technology and communicating with your clients. We find it then comes almost natural and second nature to stay abreast of rapidly evolving trends in industry, because you genuinely look forward to going to work each day and interacting with all the various facets of the greatly important field of agricultural innovation and food production. Though simplistic, our advice is rather straightforward—find something you are passionate about doing and go do it.

We believe that the science of genetic engineering is seeing some revolutionary advancements taking place. The new advancements and techniques coming online in the field of gene editing are likely to lead to progress in the GM plant arena that has been unparalleled in the past. These technological innovations will bring with them increased competition among the large industry players to best utilize these new techniques to introduce desirable traits into relevant plant species. Further, with the decreased cost and ease of gene editing becoming more pronounced, we expect to see an even greater influx of smaller players in the market making significant contributions to the field and potentially introducing some novel and disruptive applications of this new technology within relatively short time periods. These new techniques may find increasing applications and acceptance for producing crops that are directly eaten by humans, such as vegetables and fruits, or directly consumed in other ways, such as by inhalation for tobacco and medical/recreational cannabis. Of course, field testing of new varieties will always be necessary, for that is the most meaningful yardstick as to their commercial importance and viability.

One aspect of practicing in this area of the law that we absolutely love is the degree to which the technological, market, and legal issues are all intertwined. There is no way for a practitioner to be competent in this field without an intimate understanding of current technology and the potential impacts that this technology holds for the industry at large. As an attorney in this field, it is imperative that we stay abreast of the current technology and that we constantly speak with our clients about ways in which they are utilizing, or anticipate utilizing, such technology. By understanding the current state of the technology and the client's relationship to such (e.g., developer of the technology, early adopter through licenses or acquisitions, or competitive with), one is able to provide sound legal advice that is grounded within the larger context of where the market currently is positioned and also where it may be heading in the future.

The definition of what constitutes a genetically modified organism is highly dynamic and its exact contours are being shaped by the next generation of genetic engineering techniques. To help clients navigate this evolving landscape, one must stay abreast of the scientific, legal, and public policy considerations attendant to this field. The world's ever increasing population and demand for food will ensure that the intersection of genetic engineering and crop species remains a central issue in the twenty-first century.

**Key Takeaways**

- Avoid errors in understanding and making mistaken assumptions by becoming thoroughly educated in the history of genetic engineering, specifically traditional plant breeding and historically non-traditional plant breeding processes. Keep in mind that what is now considered representative of well-known crops looks very little like the wild species from which these crops were derived by traditional plant breeding. In essence, there is no bright-line demarcation between what was considered traditional plant breeding and what is now termed genetic engineering. It is hard to clearly define what a "genetic engineering technique" would entail, as traditional plant breeding can be said to engineer a plant's genome. Questions must be answered as to what constitutes "modern biotechnology" and how to scientifically define what falls within or outside of a "traditional plant breeding technique."

- Proponents of GM crops list these benefits: GM crops offer increased yield potential for important food crops on a per acre basis to address the world's increased demand for food. GM crops offer the potential to decrease synthetic chemical pesticide utilization and lower the associated environmental impact. Genetic engineering permits the insertion of desirable traits into existing crop species to make them more tolerant of rising global temperature. GM crops offer the possibility of greater concentrations or higher quality of desirable plant products, such as nutrients, specialty starches, oils, etc.
- Devote more time to reading in the relevant scientific journals and the industry and legal publications. Anticipate new trends by keeping updated on advances in other, seemingly unrelated technologies, to guide clients in out-of-the-box thinking about emerging opportunities and challenges.
- Communicate and interact with clients to stay on top of advances and keep your knowledge and understanding of the field current. Regular on-site client visits foster deeper relationships between attorney and client, and promotes understanding of the field from the client's perspective.

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