Living in a GMO World: Food and Feed Safety

Wayne A. Parrott, PhD
University of Georgia
Department of Crop and Soil Sciences
Center for Applied Genetic Technologies
Athens, GA
wparrott@uga.edu

Defining the GMO World

Genetically modified organisms (GMOs) are everywhere, or at least, so it seems! Their presence and use in food has become a heated topic due to health concerns among claims of the public's right to know. The term GMO refers to an organism that was modified in a laboratory using recombinant DNA (rDNA) technology to the exclusion of other modification methods. Such rDNA technology has been used to develop numerous genetically modified microorganism strains for use in medicine and the food industry. Such technology is widespread, and outside groups such as Greenpeace, is generally not controversial.

Glossary of Abbreviations
FDA: Food and Drug Administration
GMO: Genetically Modified Organism
OECD: Organisation for Economic Co-Operation and Development
rDNA: Recombinant DNA

A few GM animals also are in existence, but primarily for the production of high-value pharmaceuticals in their milk or egg whites. In the West, only one engineered animal, an Atlantic salmon, has been approved for human consumption, but it is not commercially available. The main spotlight and controversy centers on GM crops. Their cultivation started in 1994, and official records have been maintained since 1996. The cumulative area planted since then[1] is larger than the U.S. and Canada combined. Thus, there are data collected over the past 20 years over a huge land area that can be used to address safety issues in actual practice.

Table 1. Crops currently or soon to be commercially available

Global Status of GM Crops in 2016	
GM Crops Currently Sold in the U.S.	
Alfalfa	Papaya (Hawaiian)
Canola	Soybean
Corn	Squash/Zucchini
Cotton	Sugar Beet
GM Crops Approved and Ready for Market	
Apple	Potato
GM Crops Grown in Other Countries	
Bean	Brazil
Eggplant	Bangladesh
Rice	Iran

As seen in Table 1, the greatest variety of GM crops continues to be grown in the U.S. Corn, cotton, soybean, and canola are also grown in other countries, while Brazil, Bangladesh and Iran have their own self-developed crops. Two of these crops, corn and soybean, are almost ubiquitous ingredients in food and feed, to the point it is estimated that some 80% of the items in the typical supermarket contain ingredients derived from GM corn or GM soybean. In contrast, despite multiple claims to the contrary, GM wheat and tomatoes are not commercially available.

In the Beginning

Except for nuts, most of the produce found in a supermarket does not exist in the wild. Just like dogs have evolved from wolves, the crop varieties found in a supermarket have been derived from wild plants over the past millennia. In many cases, it is very difficult to recognize their wild versions.[2] Some, like cabbage and cauliflower, did not exist until 400 to 600 years ago. Brussels sprouts and orange carrots have only been around for some 300 years. Likewise, modern strawberries did not come into being until the mid-1700s.

Figure 1. A bowlful of wild carrots

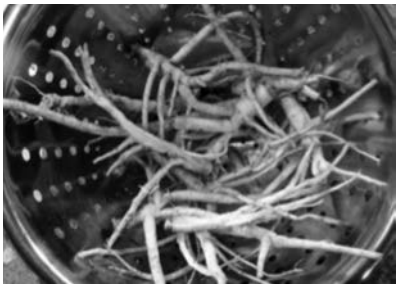

Photo: *ecolibrary.org*

Much of this change took place through the selection and crossbreeding of spontaneous mutations that appeared from time to time. It is important to remember that for the most part, it is not possible to change the appearance of something without changing the DNA inside, so all these changes have been accompanied by changes in DNA.

By the middle of the past century, breeders were no longer content to wait for desirable mutations to be found and started deliberately mutagenizing plants with ionizing radiation or

From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

Figure 2. An ad from *Popular Science*, 1961, heralding the use of mutagenesis

chemicals. Today, over 3,000 crop varieties derived from mutagenesis are in use.[3]

At the same time, breeders resorted to extraordinary methods to obtain genes from related species using a broad range of procedures to enable crosses that could not occur otherwise.[4] Although dozens of these remain in common use, to this day no one has any idea as to what genes may have been transferred to crops. None of these gene transfers has been safety tested; most relevantly, no safety issues have ever been reported as a result of these gene transfers.

The Era of Recombinant DNA

The advent of recombinant DNA technology (genetic engineering) eliminated many of the limitations associated with interspecific gene transfer and essentially made every gene on the planet accessible for transfer into plants. It is these products obtained by recombinant DNA that are referred to as "GMOs."

This technology was accompanied by a presumption that inserting DNA into a genome came with a small chance that such an insertion could alter gene expression in ways that resulted in a food or feed hazard through the production of a toxin.[5] Therefore, precautionary measures were taken to prevent such an occurrence. This resulted in global food testing standards under the auspices of the Organisation for Economic Co-Operation and Development (OECD) and the Codex Alimentarius (food code). In addition to OECD and the Codex, several countries have their own testing requirements. The overall standard is that a GM crop must be at least as safe as its conventional counterpart.

Despite the tendency of the media to treat GM crops and foods as if they were one thing, GM crops really encompass a diversity of genes and traits. Although there are universal safety testing guidelines, it is important to remember that any given trait in any given crop can pose unique hazards, and that these are evaluated on a case-by-case basis.

It is worth emphasizing that in today's global economy, any farm commodity can find its way to virtually any country. Given that no product may enter the marketplace unless it has been shown to be innocuous, safety testing and marketing approval are needed in all major importing countries. For the most part, a GM plant will not reach the marketplace until marketing approvals are in place in importing countries; otherwise, produce shipments containing unapproved events have been rejected at port with the ships sent to other destinations at great expense. The result is that a very high level of redundancy takes place in safety evaluations by all major importing countries.

Determining Food and Feed Safety

The premise behind safety testing is based on the fact that whenever two items are identical in every way, one cannot be safe and the other dangerous. If one of the two items is modified such that it is no longer safe, the lack of safety has to come from something added during the change and not from something that was already there.

Therefore, the first step in safety testing is to do a compositional analysis of the plants to determine if there is anything that was not there before. Any differences identified are then tested for safety.[6,7]

As far as changes go, GM crops are created by adding DNA to a plant. The result will confer a new and desirable trait to the plant by either turning off the expression of a plant gene or by expressing a protein. The resulting changes are divided into one of two categories.

Intentional changes include the production of the transgenic protein, if there is one, and any associated metabolites. Thus, safety testing of the intended changes centers primarily on ensuring the safety of the transgenic protein.[8] Allergenicity is a concern when it comes to proteins, leading to oft-repeated claims such as a peanut gene in lettuce could kill an unsuspecting person. Regardless, the transgenic protein is subjected to a battery of tests that minimize the probability that the protein will cause allergies.[9] Thus far, no glycosylated protein has ever been approved. Those proteins approved have been heat-labile and readily digested (>90% in 2 minutes) to minimize the chance that the protein can reach the intestine, where it would be recognized by the immune system, triggering an allergic response. In addition, approved proteins must lack a significant homology to known allergenic proteins and not be recognized by antibodies in human blood serum samples.

Toxicity is another property associated with a small number of protein families. Accordingly, transgenic proteins are tested for their possible toxicity.[10] Acute toxicology tests using escalating doses of purified toxins are conducted on mice. Subchronic toxicity tests also are conducted on rats, using 90-day trials. Longer tests are not recommended, as the background noise starts overwhelming any signal that may be there. Forty-two day trials whereby rapidly growing animals (usually broiler chicks) are fed the transgenic protein are sometimes conducted. The premise is that any perturbations

From the Purina Companion Animal Nutrition Summit: *Pet Nutrition: Beyond Essential*; Fort Lauderdale, FL; March 31-April 2, 2016.

from the diet can more easily be detected in a rapidly growing animal. Although originally considered another toxicological test, these trials are now considered more of a wholesomeness test.[11]

Whole-food feeding trials whereby animals are fed the GM crop itself[12] are not recommended by any safety agency, as these tests are not very sensitive, lack statistical power and incur a lot of background noise. Nevertheless, a few jurisdictions require them. The final criterion is one of nutritional equivalence. The nutritional value of the product cannot be altered. Any alteration results in a mandatory label alerting consumers that the product has a higher or lower level of a given nutrient.

Unintended changes include everything else that might happen accidentally as a result of making the intentional change. As mentioned previously, there is concern that plants may have genes for toxin production, and that these genes would get turned on when there is a DNA insertion. Thus, the task at hand is to find evidence of such a toxin being produced.

The challenge in testing for unintended changes centers on the need to find something that may or may not be there and if present could be present in any amount and could have any type of chemical composition. Part of the challenge is answered by monitoring plant growth in replicated field trials on the premise that an altered chemical composition in the plant might affect its growth rate or development. In addition, the crop is subjected to a compositional analysis of all its key metabolites.[13] The premise is that the shunting of metabolites toward the production of a toxin in toxicologically relevant levels would be detectable by a change in the amount of one or more relevant levels.[14] Collectively, this approach has been termed substantial equivalence, while the Food and Drug Administration (FDA) calls it a comparative safety analysis. As of this writing, the FDA has examined 147 GM crops and never found evidence of an unintended toxin production.[15]

Besides testing for food and feed safety, an environmental safety assessment is also required, but environmental issues are outside the scope of this review. Collectively, the required food/feed and environmental safety testing can take over a decade and is very expensive. The estimate is that global approval for a protein-producing crop exceeds $34 million.[16] Such an investment can only be recovered for globally grown crops and traits. GM versions of locally relevant crops or traits have been kept off the market due to prohibitive regulatory costs.

Conclusions

Twenty years into their commercialization, GM crops are the most studied foods and feeds in history. Safety testing is based on the absence of anything in the food and feed that was not there before and on the complete testing of the transgenic protein and its metabolites to ensure these do not pose any safety issues.

Nevertheless, there has been a slow but steady number of claims of adverse health effects to people and animals since the introduction of these crops. To date, not a single one of these claims has been validated. Instead, it has been possible to explain these reports as based on hearsay, shoddy experimentation,[17] inadequate statistical analyis[18] that invalidates the results, and even outright fabrication.[19]

After 20 years of widespread use in animal feed, it becomes possible to ask if their use has affected animal production in any way. A recent review[20] covering the first 18 years of the technology noted that about 95% of the feed fed to livestock is GM and that about 9 billion animals have been raised each year on GM feed without any adverse effect in their development or productivity. This estimate includes the breeder stocks that now represent multiple generations raised on GM feed without adverse effects.

At the same time, the environmental and economic aspects of GM crops are easy to measure, which make it obvious why farmers have embraced their labor and cost-saving aspects.[21] While environmental impact and safety assessment were outside the scope of this review, suffice it to say that many GM crops have been recognized for their ability to reduce soil erosion and decrease insecticide use.[22] Yet, despite their track record, the future of GM crops is becoming uncertain. Since their inception, GM crops have been the most rapidly adopted technology in the history of agriculture; however, whether GM crops will continue to play an important role in agriculture really depends on the extent to which the public becomes confident of their safety and comfortable with their use.

References

1. James C. Global Status of Commercialized Biotech/GM Crops. ISAAA Brief No. 49. International Service for the Acquisition of Agri-Biotech Applications. Ithaca, New York. 2015.

2. Weber N, Halpin C, Hannah LC, et al. Crop Genome Plasticity and Its Relevance to Food and Feed Safety of Genetically Engineered Breeding Stacks. *Plant Physiol*. 2013;161:1587-1594.

3. Joint FAO/IAEA Mutant Variety Database. International Atomic Energy Agency. *http://mvgs.iaea.org/AboutMutantVarieties.aspx*

4. Hajjar R, Hodgkin T. The Use of Wild Relatives in Crop Improvement: A Survey of Developments Over the Last 20 Years. *Euphytica*. 2007;56:1-13.

5. Kessler DA, Taylor MR, Maryanski JH, et al. The Safety of Foods Developed by Biotechnology. *Science*. 1992 256:1747-1749.

6. Kuiper HA, Kleter GA, Noteborn HP, et al. Assessment of the Food Safety Issues Related to Genetically Modified Foods. *Plant J*. 2001;27:503-528.

7. Cellini F, et al. Unintended Effects and Their Detection in Genetically Modified Crops. *Food Chem Toxicol*. 2004;42; 1089-1125.

8. Delaney B, et al. Evaluation of Plant Protein Safety in the Context of Biotechnology. *Food Chem Toxicol*. 2008;46: S71-S97.

9. Goodman RE, Panda R, Ariyarathna H. Evaluation of Endogenous Allergens for the Safety of Genetically Engineered Crops: Review of Potential Risks, Test Methods, Examples and Relevance. *J Agr Food Chem*. 2013;61:8317-8332.

10. Hammond B, Kough J, Herouet-Guicheney C, et al. Toxicological Evaluation of Proteins Introduced into Food Crops. *Crit Rev Toxicol*. 2013;43(Suppl. 2):25-42.

11. Van Haver E, et al. Safety and Nutritional Assessment of GM Plants and Derived Food and Feed: The Role of Animal Feeding Trials. *Food Chem Toxicol*. 2008;46:S2-S70.

12. Bartholomaeus A, Parrott W, Bondy G, et al. The Use of Whole Food Animal Studies in the Safety Assessment of Genetically Modified Crops: Limitations and Recommendations. *Crit Rev Toxicol*. 2013;43(Suppl 2):1-24.

13. Brune PD, Hendrickson-Culler A, Ridley WP, et al. Safety of GM Crops: Compositional Analysis. *J Agr Food Chem*. 2013; 61:8243-8247.

14. König A, et al. Assessment of the Safety of Foods Derived from Genetically Modified (GM) Crops. *Food Chem Toxicol*. 2004;42:1047-1088.

15. Biotechnology Consultations on Food from GE Plant Varieties. Food and Drug Administration. *http://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon* (Accessed Jan. 26, 2016)

16. McDougall P. The Cost and Time Involved in the Discovery, Development and Authorization of a New Plant Biotechnology Derived Trait. 2011. *http://www.croplife.org/PhillipsMcDougall Study*

17. Arjó G, Portero M, Piñol C, et al. Plurality of Opinion, Scientific Discourse and Pseudoscience: An In-Depth Analysis of the Séralini, et al., Study Claiming That Roundup® Ready Corn or the Herbicide Roundup® Cause Cancer in Rats. *Transgenic Res*. 2013;22:255-267.

18. Panchin AY, Tuzhikov AI. Published GMO Studies Find No Evidence of Harm When Corrected for Multiple Comparisons. *Crit Rev Biotechnol*. 2016. (Published online first: doi: 10.3109/07388551.2015.1130684.)

19. Abbott A. GM-Crop Papers Spark Probe. *Nature*. 2016; 529:268-269.

20. Van Eenennaam AL, Young AE. Prevalence and Impacts of Genetically Engineered Feedstuffs on Livestock Populations. *J Anim Sci*. 2014;92:4255-4278.

21. Brookes G, Barfoot P. Global Income and Production Impacts of Using GM Crop Technology 1996-2013. *GM Crops Food: Biotechnol Agri Food Chain*. 2015;6:13-46.

22. Brookes G, Barfoot P. Environmental Impacts of Genetically Modified (GM) Crop Use 1996-2013: Impacts on Pesticide Use and Carbon Emissions. *GM Crops Food: Biotechnol Agri Food Chain*. 2015;6:103-133.