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Unintended Compositional Changes in Genetically Modified (GM) Crops: 20 Years of Research

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ABSTRACT: The compositional equivalency between genetically modified (GM) crops and nontransgenic comparators has been a fundamental component of human health safety assessment for 20 years. During this time, a large amount of information has been amassed on the compositional changes that accompany both the transgenesis process and traditional breeding methods; additionally, the genetic mechanisms behind these changes have been elucidated. After two decades, scientists are encouraged to objectively assess this body of literature and determine if sufficient scientific uncertainty still exists to continue the general requirement for these studies to support the safety assessment of transgenic crops. It is concluded that suspect unintended compositional effects that could be caused by genetic modification have not materialized on the basis of this substantial literature. Hence, compositional equivalence studies uniquely required for GM crops may no longer be justified on the basis of scientific uncertainty.

KEYWORDS: *transgenic, GM, composition, equivalence, unintended*

INTRODUCTION

Investigating the compositional equivalence between genetically modified (GM) crops (crop varieties developed using recombinant DNA techniques) and nontransgenic comparators has been a cornerstone of the safety evaluation of GM crops since this approach was first suggested in 1993.[1] Compositional equivalence testing for GM crops is designed to investigate the potential unintended effects of engineering a genetic construct into a crop plant using the modern biotechnological method of transgenesis. This complements safety testing that focuses on intended effects such as the presence of the inserted DNA and the resulting RNA and proteins transcribed and expressed by a GM crop. DNA and RNA are not considered food safety risks and, thus, the safety assessment for intended effects is centered on the evaluation of the intended gene products (typically proteins).[2] Research into unintended food safety risks for GM crops has primarily involved investigating potential effects relating to crop composition.[1]

The approach to evaluating the compositional equivalence of a GM crop and nontransgenic comparators has most commonly taken the form of placing replicated field trials throughout the growing regions for that crop and collecting samples of plant tissues that are used as food and feed (e.g., grain and forage). Entries in these field trials include the GM crop, a near-isogenic nontransgenic line, and sometimes one or more nontransgenic commercial reference lines. For herbicide tolerance traits, the GM line is often included as multiple entries where certain plots are treated with the herbicide to which the crop has tolerance and also in plots where this herbicide is not sprayed. Plant tissue samples are analyzed for an array of nutrients and antinutrients (typically 60−80), and statistical comparisons are performed between the GM crop and the non-GM comparator. When significant statistical differences are observed, the mean levels of the analytes in question are compared with the range of levels that are considered to be normal for the crop as a whole. If analyte levels fall outside these ranges, then the biological relevance of the compositional changes is evaluated by determining if the observed levels would be unsafe within the context of how the crop is produced and consumed.[3,4]

The most intensive design for compositional field trials has recently been prescribed by the European Food Safety Authority (EFSA).[5] According to these requirements, at least eight field sites must be used with at least four replicates per site. If the GM line contains a trait for herbicide tolerance, both sprayed and unsprayed entries must be included, in addition to a near-isogenic nontransgenic entry. Additionally, at least six nontransgenic reference lines must be included with at least three lines being represented at each field site. These reference lines are designed to assess the normal range of analytes present in the crop, and unlike other regulatory agencies' guidelines, equivalence to the crop must focus exclusively on results from these study-specific reference lines and not refer to crop composition databases or literature values.[6] These studies are required both for new transgenic events and for combined-trait products in which two approved transgenic events are bred together by traditional means.

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The precautionary compositional testing initiated 20 years ago was based on uncertainty as to the frequency and magnitude of compositional alterations that might occur due to the transgenesis process or via metabolic alteration from expressed transgenic products. The novelty of the technology made it unclear, in 1993, if the DNA insertion process itself would be more or less likely to cause unintended changes to crop composition compared with traditional breeding and if such changes might introduce novel safety risks.

Twenty years later, not only does compositional equivalence testing continue to be a cornerstone for the safety evaluation of GM crops, but expanding regulatory requirements have increased composition study costs over 10-fold during this period (from approximately U.S. $100,000 per study to over U.S. $1 million per study), and further expansions, such as measurement of endogenous allergen levels, have been suggested.[7] Here we examine research that has occurred over the past two decades relative to the mechanisms that affect crop composition in GM and traditionally bred crops. This information along with empirical data on crop composition should shed light on whether it is reasonable, in 2013, to expect a greater risk of adverse compositional changes in GM crops compared with traditionally bred crops and, thus, whether it is reasonable to continue to uniquely require compositional equivalence studies for GM crops to evaluate safety.

WHAT HAVE WE LEARNED ABOUT UNINTENDED GENETIC EFFECTS IN TRADITIONALLY BRED CROPS?

Traditional (nontransgenic) breeding encompasses intraspecific crosses, wide crosses (sometimes between related species), crosses with wild relatives, tissue culture regeneration, and mutagenesis. Research over the past 20 years has revealed that these techniques commonly are associated with genetic mutations, deletions, insertions, and rearrangements.[8] In fact, for those crop species investigated, most of the genome is derived from mobile genetic elements.[9−11] Transposons, or "jumping genes", can move within the genome, causing insertional mutagenesis. In addition, over 2500 crop varieties have been generated by intentional mutagenesis (non recombinant DNA techniques), and many more have resulted from selection of spontaneous mutants.[12,13]

Although breeders have selected for and purposefully induced random changes in the DNA of plants for an extended period of time, recent molecular techniques have allowed us to understand the specific types of changes that have been incorporated into new crop cultivars. These genetic changes appear to be varied and extensive, and yet few safety issues have arisen.

WHAT HAVE WE LEARNED ABOUT UNINTENDED COMPOSITIONAL EFFECTS IN TRADITIONALLY BRED CROPS?

As crop breeders attempt to develop improved cultivars, they routinely look for individual plants that display improved agronomic characteristics. Also, plants are culled that display commercially unacceptable agronomic characteristics. If individual plants or lines display some characteristics that are improved (e.g., disease tolerance) and others that are not commercially acceptable (e.g., decreased yield), then breeders attempt to incorporate the desirable genetic basis for the improved traits into lines while eliminating the detrimental traits. Crop breeding programs have generally not focused on or monitored any resulting compositional changes that might accompany these breeding efforts, and only on rare occasions and in a few crops (e.g., white potatoes, celery, and squash) have such changes caused adverse effects.[14] These rare examples have highlighted where risks are present due to a low margin of safety with some plant constituents in specific crops. For example, white potatoes contain high levels of toxic glycoalkaloids, and up-regulation of these compounds due to traditional breeding can cause sickness. In the aforementioned case of up-regulation of glycoalkaloids, this actually occurred when endogenous insect resistance was selected for by breeders without knowledge of the mechanism for this resistance.[15] Any new variety of white potato, including any GM variety, is now routinely screened for glycoalkaloid levels, and acceptable limits have been defined. In contrast, no corn variety has been found to be compositionally unsafe, so new traditionally bred corn varieties are not routinely monitored for composition. For example, the USDA released a new non-GM insect resistance corn trait to crop breeders that was found in a rare Andean corn line without any knowledge of the mechanism for insect resistance and without any formal safety assessment.[16] This course of action is supported by a vast experience with the compositional safety of corn.

Much has been learned over the past 20 years about the compositional variation that occurs in some large-acre crops such as corn, soybean, and cotton. This has occurred, in part, as a consequence of the efforts made to evaluate the compositional safety of GM crops, which required knowledge of the normal state for traditionally bred crops. For example, the International Life Sciences Institute (ILSI) has developed a database to aid in assessing the normal variability in crop composition.[17,18] Research over the last twenty years has shown that many constituents in crop plants vary widely due to genotype but also due to growing environment and storage of the crop after harvest.[19−25]

HOW DO UNINTENDED GENETIC EFFECTS IN GM CROPS COMPARE WITH THOSE IN TRADITIONALLY BRED CROPS?

Transgenesis involves the insertion of a designed genetic cassette with a known DNA sequence intended to produce a prescribed gene product (typically a protein) to achieve a desirable trait through a known mechanism. The transgenic insert in the plant is sequenced to determine if it has been inserted as intended and to confirm that it codes for the desired gene product. The flanking endogenous plant DNA is also sequenced to understand if any native genes or regulatory elements are disrupted. Finally, the plant genome is probed to ensure that only one insertion site exists.[2,26] This contrasts with traditional breeding by which many genes are randomly recombined and/or many mutations are generated with little or no knowledge of the genetic changes that are induced or the mechanism behind the traits that are selected. It has been acceptable with traditional breeding for many undescribed genes from wild relatives with no history of safety to be incorporated into new crop varieties to obtain novel or improved agronomic traits such as pest resistance.[27]

HOW DO UNINTENDED COMPOSITIONAL EFFECTS IN GM CROPS COMPARE WITH THOSE IN TRADITIONALLY BRED CROPS?

Unintended Effects Are Expected. It is a common misconception that one should expect the composition of a GM crop to be equal to that of its near-isogenic nontransgenic comparator with the exception of intended changes. Scientific knowledge does not support this expectation. It has been demonstrated that even for elite nontransgenic commercial varieties, single-plant selections can result in marked variation in phenotype. This occurs because such lines are often not completely fixed for even the most basic traits. For example, single-plant selections from elite soybean lines can vary in seed weight, maturity, plant height, and lodging.[28] GM crops are most often generated from plants derived from single cells grown in tissue culture, as are many non-GM crops. In addition, the effects of plant protection such as that provided by insect- or disease-tolerant traits are expected to reduce the up-regulation of pathogenesis related proteins and metabolites compared with less well protected near-isoline plants.[29] Furthermore, applications of many herbicides to herbicide-tolerant GM or non-GM crops would be expected to have effects on plant composition because some plant stress from such applications is common.[30−32] Thus, a GM line, or a nontransgenic line derived from a single plant, protected from insect or diseases, or sprayed with an herbicide, would be expected to differ compositionally from the composite line from which it was derived, especially if it experiences different biotic or abiotic stress related to intended transgenic traits.

Compositional Safety Should Be Considered in the Context of the Normal Composition of the Crop. Understanding that unintended effects are expected in both GM crops and traditionally bred crops allows one to ask if such changes in GM crops are more frequent, of higher magnitude, or inherently more dangerous compared with traditionally bred crops. It also sheds some light on the common practice of looking for statistical differences as a way of detecting meaningful changes in composition between a GM line and its near-isogenic nontransgenic comparator. Regulators chose the difference-testing experimental design as a starting point,[33] but 20 years of safety testing have revealed no safety hazards using this approach (see the next section). However, it should be noted that for the purposes of a safety assessment, the question is not whether the GM line is different from its near-isogenic nontransgenic comparator but rather if it is as safe as its conventional counterpart with a history of safe consumption.[33] If the composition is generally expected to differ between any two crop lines, including a GM line and its near-isogenic nontransgenic comparator, then statistical tests for these differences simply measure the power of the experiment to detect the numerical differences that are expected to frequently occur. In the context of a safety assessment, a more relevant analysis would be to evaluate if the observed level of the compositional analyte differs meaningfully from the normal array of levels observed for the aggregate crop that has a history of safe consumption; it is this analysis that informs safety.[3] Collecting more and more data from increasingly larger studies serves only to detect more fleetingly small differences that are expected and irrelevant to safety.

Two Decades of Research Confirms That Transgenesis Is Less Disruptive of Composition Compared with Traditional Breeding. Scores of publications and regulatory submissions have confirmed the compositional equivalence between GM crops and their conventional counterparts and their equivalent safety. Over the past 20 years, the U.S. FDA found all of the 148 transgenic events that they evaluated to be substantially equivalent to their conventional counterparts, as have the Japanese regulators for 189 submissions, with the latter including combined-trait products.[34,35] Over 80 peer-reviewed publications also conclude this same compositional safety for GM crops.[4,36−118] These studies have spanned the crops of corn, soybean, cotton, canola, wheat, potato, alfalfa, rice, papaya, tomato, cabbage, pepper, raspberry, and a mushroom, and traits of herbicide tolerance, insect resistance, virus resistance, drought tolerance, cold tolerance, nutrient enhancement, and expression of protease inhibitors. In addition, numerous studies have found that variation resulting from traditional breeding and environmental factors dwarf any changes observed in the composition due to introducing a trait through transgenesis (see previous citations).

HOW MUCH UNCERTAINTY REMAINS AFTER 20 YEARS OF RESEARCH?

After two decades of compositional equivalence studies, it seems reasonable to evaluate the scientific knowledge that has been gained relative to the frequency and magnitude of compositional changes for GM and traditionally bred crops. We have cited many of these studies here to facilitate examination of these empirical results by others. It is also reasonable to assess our current knowledge of the genetic mechanisms that underlie these changes in both traditionally bred and GM crops. Our assessment is that there appears to be overwhelming evidence that transgenesis is less disruptive of crop composition compared with traditional breeding, which itself has a tremendous history of safety. Whether this is the interpretation of other scientists, it certainly seems reasonable to evaluate the evidence that has been amassed over the past 20 years to determine if sufficient uncertainty still exists such that the many millions of dollars spent each year on compositional studies with GM crops can still be generally justified in 2013 or, alternatively, whether such studies should be hypothesis-driven on the basis of reasonable and unique risks posed by the novelty of certain traits (e.g., intentionally modified biochemical pathways). This is especially important as we try to feed a rapidly growing global population and the use of GM technology to improve crop production and nutrition becomes increasingly restricted from public sector researchers due to insurmountable regulatory costs. Improvements in crops for developing countries will almost certainly fall to public sector researchers, who are now putting existing transgenic events on the shelf and discontinuing the development of new projects due to escalating regulatory costs. We encourage the greater scientific community to evaluate the current state of knowledge regarding compositional safety risks of transgenic crops. The merits of continuing to generally require compositional analysis of GM crops to inform safety seems dubious given the results of 20 years of research, and if agreement can be reached that these studies are no longer warranted, use of this technology will become accessible to a wider array of scientists.

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Notes

The authors declare the following competing financial interest(s): RH is employed by Dow AgroSciences which develops and sells GM crop seed. WP is retired from the US FDA and thus his views do not necessarily represent those of the agency.

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