

Compositional assessment of transgenic crops: an idea whose time has passed

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Compositional studies comparing transgenic crops with non-transgenic crops are almost universally required by governmental regulatory bodies to support the safety assessment of new transgenic crops. Here we discuss the assumptions that led to this requirement and lay out the theoretical and empirical evidence suggesting that such studies are no more necessary for evaluating the safety of transgenic crops than they are for traditionally bred crops.

Compositional equivalence is considered a cornerstone of the case-by-case safety assessment for transgenic crops. Following this procedure, the composition of a transgenic crop is compared with that of non-transgenic comparators that have a history of safe consumption. When compositional equivalence is established between the endogenous components of transgenic and non-transgenic crops, the safety assessment can focus on properties of the gene products expressed by the transgenes [1]. If compositional differences are noted, the safety implications of the differences are assessed. For input traits, gene products are typically functional proteins that adversely affect a crop pest or confer herbicide tolerance. These genes are not normally expected to affect biochemical pathways or cascades.

An underlying assumption for selectively evaluating transgenic crops with input traits for compositional changes, while not investigating further the safety of conventionally bred crops, is that some unknown phenomenon associated with the transformation of plants or the expression of transgenes is more likely to alter the composition of plants in a different or more intense way than for new varieties produced by traditional breeding techniques or by crossing with wild crop relatives. The further assumption here is that the insertion of one, or a small number, of well-characterized transgenes is more likely to produce an unexpected adverse change in the composition of a crop than does the movement of hundreds or thousands of uncharacterized genes as occurs in conventional breeding. An additional assumption supporting the compositional analysis of transgenic input traits is that such compositional changes would not be readily detectable from the phenotypic evaluations used for both the selection of commercially viable transgenic events and for the selection of commercial lines from traditional breeding programs.

Such agronomic evaluations are conducted as a routine part of the development process designed to bring viable new crop selections to market.

Insertional mutagenesis and the potential formation of fusion proteins are real possibilities during the insertion of transgenes, but are even more likely during traditional breeding when many genes must recombine. Such changes are readily observable in “off types” during traditional breeding and even within commercial non-transgenic crop fields. Even so, molecular studies with transgenic crops are required to characterize the flanking DNA regions of transgenic inserts to investigate if endogenous genes have been disrupted, and also to determine if open reading frames for alternative proteins are present and represent a safety concern. Such studies are not conducted for traditionally bred crops and have not compromised their safety.

While most scientists consider the “adverse-composition” hypothesis to be highly unlikely [2,3], new technologies always demand more scrutiny compared with more established techniques. For this reason, many compositional equivalence studies have been completed with transgenic crops (e.g. corn, cotton, soybean, wheat, rice, potato) over the last decade, and the results published in peer-reviewed scientific journals (see Box 1). In all cases, the composition reported for the transgenic crops was equivalent to that of their non-transgenic counterparts with the exception of intended changes. One consequence of this research has been that the normal variation of compositional components of several common crops has been characterized for the first time. The large variability in the normal composition of many non-transgenic crop components is clear, yet these crops are considered safe to eat [4–7]. It is noteworthy that some crops, such as potato and lima bean, have known endogenous components that, when present in high concentrations, can be toxic to humans and animals. For this reason, new varieties of these crops are routinely screened for these components independent of the method used to generate the new variety [8,9].

With no real mechanism identified that implicates transgenes as more likely to adversely affect crop composition compared with traditional plant breeding methods, and with over a decade of experience indicating that significant compositional changes are absent for transgenic crops expressing input traits, should compositional equivalence data still be required by regulatory agencies? This is a particularly timely question as

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Box 1. Published compositional equivalence studies with transgenic crops**Maize**

Drury, S.M. *et al.* (2008) Composition of forage and grain from second-generation insect-protected corn MON 89034 is equivalent to that of conventional corn (*Zea mays* L.). *J. Agric. Food Sci.* 56, 4623-4630.

George, C. *et al.* (2004) Composition of grain and forage from corn rootworm-protected corn event MON 863 is equivalent to that of conventional corn (*Zea mays* L.). *J. Agric. Food Sci.* 52, 4149-4158.

Herman R.A. *et al.* (2004) Compositional equivalence of Cry1F corn event TC6275 and conventional corn (*Zea mays* L.) *J. Agric. Food Sci.* 52, 2726-2734.

Herman, R.A. *et al.* (2007) Compositional assessment of event DAS-59122-7 maize using substantial equivalence. *Reg. Tox. Pharm.* 47, 37-47.

McCann, M.C. *et al.* (2007) Comparison of forage and grain composition from insect-protected and glyphosate-tolerant MON 88017 corn to conventional corn (*Zea mays* L.) *J. Agric. Food Sci.* 55, 4034-4042.

Sidhu, R.S. *et al.* (2000) Glyphosate-tolerant corn: the composition and feeding value of grain from glyphosate-tolerant corn is equivalent to that of conventional corn. *J. Agric. Food Sci.* 48, 2305-2312.

Ridley, W.P. *et al.* (2002) Comparison of the nutritional profile of glyphosate-tolerant corn event NK603 with that of conventional corn (*Zea mays* L.). *J. Agric. Food Sci.* 50, 7235-7243.

Soybean

Harrigan, G.G. *et al.* (2007) Chemical composition of glyphosate-tolerant soybean 40-3-2 grown in Europe remains equivalent with that of conventional soybean (*Glycine max* L.) *J. Agric. Food Sci.* 55, 6160-6168.

Lundry, D.R. *et al.* (2008) Composition of grain, forage, and processed fractions from second-generation glyphosate-tolerant soybean, MON 89788, is equivalent to that of conventional soybean (*Glycine max* L.) *J. Agric. Food Sci.* 56, 4611-4622.

McCann, M.C. *et al.* (2005) Glyphosate-tolerant soybeans remain compositionally equivalent to conventional soybean (*Glycine max* L.) during three years of field testing. *J. Agric. Food Sci.* 53, 5331-5335.

Padgett, S.R. *et al.* (1996) The composition of glyphosate-tolerant soybean seeds is equivalent to that of conventional soybeans. *J. Nutr.* 126, 702-716.

Taylor, N.B. *et al.* (1999) Compositional analysis of glyphosate-tolerant soybeans treated with glyphosate. *J. Agric. Food Sci.* 47, 4469-4473 (1999).

Zhu, J. *et al.* (2008) Transcriptome response to glyphosate in sensitive and resistant soybean. *J. Agric. Food Sci.* 56, 6355-6363.

Cotton

Berberich, S.A. *et al.* (1996) The composition of insect-protected cottonseed is equivalent to that of conventional cottonseed. *J. Agric. Food Sci.* 44, 365-371.

Hamilton, K.A. *et al.* (2004) Bollgard II cotton: compositional analysis and feeding studies of cottonseed from insect-protected cotton (*Gossypium hirsutum* L.) producing the Cry1Ac and Cr2Ab2 proteins. *J. Agric. Food Sci.* 52, 6969-6976.

Tang, M. *et al.* (2006) Absence of effect after introducing *Bacillus thuringiensis* gene on nutritional composition in cottonseed. *J. Food Sci.* 71, S38-S41.

Potato

Catchpole *et al.* (2005) Hierarchical metabolomics demonstrates substantial compositional similarity between genetically modified and conventional potato crops. *Proc. Nat. Acad. Sci.* 102, 14458-14462.

El-Khishin *et al.* (2009) Assessment of genetically modified potato lines resistant to potato virus Y using compositional analysis and molecular markers. *Res. J. Agric. Biol. Sci.* 5, 261-271.

Esposito, F. *et al.* (2002) Glycoalkaloid content and chemical composition of potatoes improved with nonconventional breeding approaches. *J. Agric. Food Sci.* 50, 1553-1561.

Wheat

Baker, J.M. *et al.* (2006) A metabolomic study of substantial equivalence of field-grown genetically modified wheat. *Plant Biotech. J.* 4, 381-392.

Obert, J.C. *et al.* (2004) The composition of grain and forage from glyphosate tolerant wheat MON 71800 is equivalent to that of conventional wheat (*Triticum aestivum* L.) *J. Agric. Food Sci.* 52, 1375-1384.

Rice

Oberdoerfer, R.B. *et al.* (2005) Rice (*Oryza sativa* L.) containing the *bar* gene is compositionally equivalent to the nontransgenic counterpart. *J. Agric. Food Sci.* 53, 1457-1465.

Alfalfa

McCann, M.C. *et al.* (2006) Glyphosate-tolerant alfalfa is compositionally equivalent to conventional alfalfa (*Medicago sativa* L.) *J. Agric. Food Sci.* 54, 7187-7192.

Raspberry

Malowicki, S.M.M. *et al.* (2008) Comparison of sugars, acids, and volatile composition in raspberries and the wild type 'Meeker' (*Rubus idaeus* L.) *J. Agric. Food Sci.* 56, 6648-6655.

regulators continue to propose more complex and onerous requirements for conducting compositional equivalence studies [10]. It is also paradoxical that, after more than a decade of safe use, regulators propose even more stringent safety assessment without providing clear scientific justification.

If the role of governmental regulatory agencies is to evaluate the safety of transgenic crops, rather than to placate the fears of consumers, then there appears to be little validity in continuing to uniquely require compositional data for new transgenic varieties. As mentioned above, investigations of this type, aimed at evaluating safety, should be restricted to potentially deleterious constituents that are known to be present in some crop varieties at concentrations that can impact safety. It is counter-intuitive for regulators to try to regain the confidence of the public with regards to their scientific rigor by taking scientifically unsupportable actions. Increased regulatory scrutiny may also send the unintended message that regulators have heightened safety concerns.

As traits are brought forward that are designed to affect or regulate biochemical pathways and cascades, directed hypothesis-driven compositional studies may well be warranted. However, the current complexity and resource requirements for compositional studies on transgenic crops containing input traits are not justified by a commensurate understanding of safety. These resources seems especially worthy of mention in this time of rising food prices and food shortages in developing countries. Unwarranted regulatory hurdles act as a barrier to innovation. This is especially the case for researchers with limited resources working with specialty crops, where the cost of bringing technology to market may not be justified if regulations are unnecessarily onerous. Compositional equivalence for transgenic crops expressing input traits appears to be an idea that has outlived its usefulness.

Disclosure statement

R.A. Herman is employed by Dow AgroSciences LLC, a wholly owned subsidiary of The Dow Chemical Company,

which develops transgenic crops and produces insecticides, herbicides, and fungicides for agricultural applications and residential pest control. B.M. Chassy and W. Parrott declare no conflict of interest.

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