



Short communication

Endogenous allergens in the regulatory assessment of genetically engineered crops



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ABSTRACT

A scientific approach to the assessment of foods derived from genetically engineered (GE) crops is critical to maintaining objectivity and public confidence in regulatory decisions. Principles developed at the international level support regulators and enable robust and transparent safety assessments. A comparison of key constituents in the GE crop with a suitable comparator is an important element of an assessment. In Europe, endogenous allergens would be included in the comparative analysis, however this approach has been hindered by technical limitations on the ability to accurately measure identified allergenic proteins. Over recent years, improved proteomic methods have enabled researchers to focus on major allergenic proteins in conventional food crops, as information on natural variability is largely lacking. Emerging data for soybean indicate that variability in levels of major allergens already in the food supply is broad. This raises questions about the biological interpretation of differences between a GE plant and its conventional counterpart, in particular, whether any conclusions about altered allergenicity could be inferred. This paper discusses the scientific justification for requiring proteomic analysis of endogenous allergens as part of the evaluation. Ongoing scientific review and corresponding international discussion are integral to ensuring that data requirements address legitimate risk assessment questions.

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1. Introduction

Foods derived from genetically engineered crops, also referred to as genetically modified (GM) foods, have been in the food supply for almost two decades. In a majority of countries, authorisation or approval of GE foods is required before products can enter commercial markets. This pre-market approval process is contingent upon a scientific assessment to ensure that foods produced from the GE plants are as safe for human consumption as the conventional counterpart foods. Based on international expert consultations convened in the early 1990s, the World Health Organisation (WHO) and the Organisation for Economic Cooperation and Development (OECD) produced strategies and principles to underpin the safety assessment of GE foods (WHO, 1991; OECD, 1993). Later, a specialist taskforce of the Codex Alimentarius Commission elaborated guidance to support these principles and strategies, and facilitate their application to GE food regulation at the international level (Codex Alimentarius, 2009). Subsequently, the Codex guidelines have been widely adopted and used as the foundation for

assessment protocols implemented in many countries with an established food regulatory system. As a result, there is broad consensus on the approach to GE food assessment based on sound scientific principles.

As outlined in the Codex guidelines, a food safety assessment includes a detailed compositional analysis of the GE plant and a suitable control, typically from a near-isogenic line (Codex Alimentarius, 2009). The European Food Safety Authority (EFSA) has advanced the view that key allergens be included in the comparative analyses, particularly for allergenic crops such as soybean (EFSA, 2011, 2012). The rationale is that changes in the levels of these proteins might indicate altered allergenicity of the GE plant, an unintended effect resulting from the genetic modification (Fernandez et al., 2013; Spök et al., 2005). The Codex guidelines do not elaborate the toxicological or nutritional basis for including endogenous allergens in the compositional analyses of GE crops (Codex Alimentarius, 2003).

The focus on endogenous allergens in a comparative assessment reflects a continuing level of public and academic interest in allergenicity (Breiteneder and Mills, 2005). However, for a majority of agronomic traits such as herbicide tolerance and insect resistance, significant changes in GE plant composition are generally not predicted from the insertion of genes that otherwise are well

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characterised. Moreover, excluding effects from newly introduced proteins, there are no reports in the literature of altered allergenicity in a GE plant as an unintended consequence of transgene insertion (Nicolia et al., 2013; Batista et al., 2005; Burks and Fuchs, 1995).

Technical limitations in analysing the relative amounts of specific proteins in large numbers of samples are well documented (Panda et al., 2013; Stevenson et al., 2012; Burks and Fuchs, 1995). In recent years, new analytical techniques with improved sensitivity and specificity have made it possible to detect small changes in the levels of plant proteins (Houston et al., 2011), making comparative analyses of endogenous allergens apparently more feasible. At the same time, these developments have brought into focus a more fundamental question about the utility of this information for assessment purposes, specifically whether fluctuations in the levels of allergenic proteins can be correlated with changes in the allergenicity of the whole plant. This paper explores the scientific justification for requiring proteomic analysis of endogenous allergens as part of the safety assessment of genetically modified food.

2. The comparative approach

An important element of GE food assessments is that foods with a history of human consumption are an appropriate benchmark for safety. The comparative approach uses data from a suite of laboratory studies and field trials to determine compositional differences between the GE plant and a suitable comparator. This information aids in the identification of potential safety and nutritional issues, for further consideration in the safety assessment.

The purpose of analysing the composition of both GE and conventional plants for a comparative assessment is twofold. Firstly, it is used to determine if the genetic modification process itself has resulted in any unexpected changes in the composition of the GE plant, with particular focus on those parts of the plant used as food. Secondly, the compositional analysis will confirm the intended effect where the modification has deliberately introduced a new nutrient or significantly changed the level of one or more key nutrients, either through the expression of introduced gene products, or as a result of targeted manipulations to metabolic pathways in the GE plant. In these cases, more detailed nutritional studies may be relevant (Codex Alimentarius, 2009 Annex 2), and could involve limited testing of the GE food in animal feeding studies or, more likely, in human volunteers.

3. Compositional analysis

The compositional analysis requires statistical data on defined and quantifiable parameters such as proteins, carbohydrates, fibre, moisture, amino acids, fatty acids, vitamins and minerals. As well as considering key constituents, the analysis includes known endogenous anti-nutritional components and natural toxicants characteristic of the plant species. These data allow primary differences in composition between the GE plant and comparator to be identified and subsequently assessed for a possible impact on human health. However, to be relevant for consumer safety, any compositional changes in a GE plant must be biologically meaningful, that is, they would need to fall outside of the range of natural variation to warrant further investigation.

Determining whether changes in the GE plant have biological meaning necessarily requires baseline data on the natural variability in crop composition in commercial cultivars already in the food supply. Historically, these have been the products of conventional breeding, however for some crops, GE cultivars have become more commercially prevalent over time. Fluctuations in key constituents

are associated with both genetic and environmental influences (Stevenson et al., 2012), therefore in principle, for high-yielding crop plants that are phenotypically normal, a range of levels for any constituent is accepted as normal biological variation.

4. Applying the comparative approach to endogenous allergens

In theory, introducing genetic changes into a food-producing plant could increase or decrease endogenous protein synthesis, even for simple modifications such as herbicide tolerance, where significant compositional changes would not be expected (Goodman and Tetteh, 2011). While this is considered to be unlikely, a compositional analysis of key constituents can determine whether unintended changes which do not affect agronomic performance have occurred. The question for risk assessors is whether the comparison is strengthened by inclusion of a subset of proteins, the endogenous allergens, particularly in crops already recognised as allergenic and regulated as such (Panda et al., 2013).

Undertaking a comparative assessment of endogenous allergens assumes that, for any plant species, a relevant set of major allergenic proteins has been identified and at least partially characterised. For data analysis, it assumes that their levels can be accurately and reproducibly measured. The approach also assumes that any differences can be unequivocally attributed to the genetic modification and, most importantly, that risk to public health as a result of the differences has either increased or decreased accordingly. Any potential impact on both allergic and non-allergic populations must be considered separately.

5. Crops with known allergens

The development of sensitive, high throughput, quantitative techniques has facilitated investigation of a number of partially characterised allergenic proteins and their expression variability in some major food crops. The information emerging from proteomic studies is that natural variation in conventional plants is broad, and much greater than any differences likely to be found between GE and near-isogenic or parental lines grown under similar agricultural conditions.

Research efforts have focused on the seed proteins of soybean (*Glycine max*) due to its known allergenicity (Cordle, 2004; Savage et al., 2010; Stevenson et al., 2012) and the existence of many GE varieties (Doerrer et al., 2010; Houston et al., 2011). Similar information on differential expression of proteins in maize (*Zea mays*) and rice (*Oryza sativa*) is becoming available, although these food crops are not recognised as major allergens (Fonseca et al., 2012; Panda et al., 2013).

Soybean allergy primarily affects young children, the majority of whom will eventually outgrow their allergy (Savage et al., 2010). To investigate the natural range of prominent seed storage proteins in soybean, Houston et al. (2011) conducted a detailed quantitative analysis of 10 known allergens in 20 non-GE commercial soybean varieties that were considered to be representative of the germplasm grown by U.S. farmers. At least 37 soybean proteins in the Food Allergy Research and Resource Program (FARRP) database are associated with food allergies. To date, eight allergenic soybean proteins have been characterised (IUIS Allergen Nomenclature Sub-Committee, 2014). Houston et al. (2011) found the expression levels amongst the 10 measured allergens, which included the major soybean glycinins, varied approximately 10-fold with some of the least abundant allergens (eg. Gly m 5; beta-conglycinin) showing the highest variability. At least a two-fold variability in four major seed allergens of low to moderate abundance was observed, with some variability up to sevenfold across the commercial varieties.

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