

CME Review

The allergenicity of genetically modified foods from genetically engineered crops



A narrative and systematic review

S. Eliza Dunn, MD^{*,†}; John L. Vicini, PhD[‡]; Kevin C. Glenn, PhD[§]; David M. Fleischer, MD^{||}; Matthew J. Greenhawt, MD, MBA, MSc^{||}

^{*} Medical Sciences and Outreach Lead, Monsanto Company, St Louis, Missouri

[†] Division of Emergency Medicine, Washington University, St Louis, Missouri

[‡] Food and Feed Safety Scientific Affairs Lead, Monsanto Company, St Louis, Missouri

[§] Allergenicity/Pipeline Issues Management Lead, Monsanto Company, St Louis, Missouri

^{||} Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the testing and safety features that genetically modified products are subject to in determining their allergenicity
- Identify the basis and rationale for genetic modification
- Review the evidence regarding genetically modified products and any association with food allergy

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Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Reprints: Matthew J. Greenhawt, MD, MBA, MSc, Assistant Professor of Pediatrics, Allergy Section, Children's Hospital Colorado, University of Colorado School of Medicine, 13123 East 16th Avenue, Box 518, Anschutz Medical Campus, Aurora, CO 80045; E-mail: Matthew.Greenhawt@childrenscolorado.org.

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S.Eliza Dunn, MD (Author)
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Introduction

During the past 2 decades, the diagnosis of food allergy has increased in industrialized countries. Immunoglobulin E (IgE) food allergies affect an estimated 4% to 8% of the American population.^{1,2} The reason for this increase remains unclear, but food allergy has become an increasingly difficult challenge for patients and their physicians to manage. Repeated exposures lead to significant morbidity, life-threatening anaphylaxis, and substantial health care costs. Because proteins are the primary precipitant of many allergic reactions, some members of the public have become concerned that the proteins produced in genetically modified (GM) crops will lead to an increase in allergic reactions in people who consume those crops. Others have made claims that these products have directly caused or contributed to the overall increase in food allergies. In addition, people worry that the introduction of a gene might increase the levels of allergenic proteins in these plants. This article describes how GM crops are produced, how GM crops are tested, and how allergies are tested and future directions for testing and GM products and presents a systematic review on GM products and their potential for allergenicity.

Part 1*What Is a GM Crop?*

Since the dawn of agriculture more than 10,000 years ago, farmers have modified plants through selective breeding to confer a benefit (yield or disease resistance) into domesticated crops

such as maize and wheat.³ At the most basic level, plant breeding involves mating at least 2 parental lines, each with at least 1 desirable characteristic, and selecting offspring that express as many of the desirable characteristics as possible while avoiding undesirable characteristics from the parental lines. The development of GM crops could be characterized as “precision breeding.” In the 1980s, modern biotechnology gave breeders an additional tool to select specific gene(s) instead of having to start with all the genes in each parental line to bring desirable traits into crops. This also allowed breeders to select genes from sources beyond those available in the target crop species. However, even this benefit of modern biotechnology is rooted in practices by ancient farmers who could create non-natural plants, such as wheat, by mating across several species.⁴

The most common sources for modifications in GM crops produce proteins that confer insect resistance or herbicide tolerance. Proteins developed for GM crops undergo extensive testing before their introduction into the development pipeline.⁵ In nature, bacteria or plants often express desirable traits that confer pest resistance. Once the gene is identified, it is inserted into a plasmid and transferred to a species of bacterium called *Agrobacterium tumefaciens*. Then, this bacterium transfers the gene into plant cells, creating a transgenic plant that expresses the desired trait.⁶ An example of this is the expression of crystal proteins produced by *Bacillus thuringiensis*. These bacteria are a natural part of the environment and produce proteins that have been used as organic insecticides and for control of mosquitoes and other disease-bearing insects for more than 50 years.⁷ These

commonly occurring proteins have never had a documented case of allergic response despite significant human exposure.^{8,9}

Genetically modified crops have been cumulatively grown on more than 4 billion acres.¹⁰ Since the introduction of GM crops in 1996, there have been no documented adverse effects in humans or animals.³ Many independent assessments of GM crops have concluded that the use of modern biotechnology to introduce new traits into crops is as safe, if not safer than, other breeding tools to improve crops.¹¹ In addition, the lack of adverse effects is due to the rigorous safety assessments that are performed before commercialization.^{3,6,12–14} A key aspect of this assessment process is to determine the allergenic potential of the crop and prevent the introduction of a known or novel allergen into the food supply. This safety assessment is further reinforced by ensuring that the level of endogenous allergens has not been significantly changed compared with the non-GM counterpart. This degree of testing is not required for non-GM crops, but it provides reassurance to the public that foods from GM crops are safe for consumption.

How Are GM Crops Assessed for Allergenicity?

Genetically modified crops undergo rigorous assessment for food, feed, and environmental safety before commercialization.^{12–14} The allergenicity assessment of GM plants includes 2 elements: (1) the assessment of the entire GM plant and (2) the assessment of the newly expressed proteins.

The key question for assessing the allergenic potential of the entire GM plant is whether the use of transgenic methods has an unintended effect on the levels of allergenic proteins native to the plant.^{12,13} Of the current 9 commercially available GM crops, soybean is the only crop that is also 1 of the 8 foods responsible for 90% of food allergy cases in the United States.¹⁵ It was a reasonable hypothesis in 1992, before direct experience with GM crops, for the Food and Drug Administration to conjecture that using transgenic methods on plants might activate dormant metabolic pathways and possibly result in the synthesis of allergens or other hazards.¹⁶ These early concerns led to guidance documents and regulations for GM crops to evaluate the safety of their intended and potential unintended effects.^{12–14} However, since 1992, more than 1,300 separate assessments by regulatory agencies around the world have reviewed safety data on various GM crops, each time concluding that the GM crop is as safe as conventionally developed crops (collated from www.biotradestatus.com when accessed on January 23, 2017). In addition, genomic sequencing of plants has shown that many possible routes for genetic change by biotechnology have parallel examples in nature, including the insertion of genes from *A tumefaciens* into plant genomes such as sweet potato.¹⁷ Furthermore, the natural variability of native allergenic proteins in conventionally bred and cultivated crops has been shown to be very large, up to 19-fold in some cases. This variability is mainly traceable to differences in environmental growing conditions at the time of grain production.^{18–21} Therefore, to date, at least 20 years of data on GM crops have shown that applying transgenic methods to plants does not affect the levels of allergenic proteins native to the particular crop, such as soybeans, outside the natural range of variation; hence, GM crops are as safe as conventionally developed crops.

The assessment of the allergenic potential of newly introduced proteins in GM crops, as outlined by Codex,¹² is built on a weight-of-evidence approach that includes the following questions:

1. Is the source of the gene known to be a common allergenic food?
2. Does the amino acid sequence of the newly expressed protein have meaningful structural similarity to known allergenic proteins?
3. Is the newly expressed protein abundant in the food?

4. Is the expressed protein highly resistant to digestion by pepsin?

The Codex guidance recommends considering all these factors together to conclude whether the newly expressed protein has a potential to be allergenic, because each component of this weight-of-evidence approach has exceptions that, in isolation, might be misleading for the risk assessment.²² Thus, each GM crop is reviewed on a case-by-case basis and the results are assessed in aggregate. This weight-of-evidence approach also is necessary because validated animal models for predicting human allergic reactions to food proteins do not exist, although many researchers have established models that allow experimentation on elements of the human allergic response.²²

Source of gene

Is the source of the gene introduced into a GM crop from a donor organism that is known to be a risk for eliciting allergic reactions in people (eg, from 1 of the 8 foods responsible for 90% of food allergy cases: soy, wheat, milk, peanuts, tree nuts, shellfish, fish, and eggs)?¹⁵ Information on past and current use, if any, of the source organism in the food supply is important to understand. Understanding the natural history of the source, as related to food safety, is critical. Because 8 foods are responsible for 90% of food allergies in the United States, it is an industry-accepted best practice to not use genes from these sources.

For example, genes from microbes and crops, such as maize and rice, are at low risk of encoding a protein that has the potential to be an allergen, because few individuals in the population have ever been known to have immediate hypersensitivity reactions.

Protein amino acid sequence

Intrinsic to the need for a weight-of-evidence approach to allergy assessments is the appreciation that using a gene from a source that is unlikely to cause allergic reactions does not mean that a specific protein from that source might not be allergenic. Conversely, only a few proteins in commonly allergenic foods are responsible for most allergic reactions to those foods. Therefore, it is critical to assess the newly expressed protein(s) in a GM crop using bioinformatic tools to compare the amino acid sequence of this protein with sequences of all known human allergens.^{23–25} These methods are designed to determine whether the newly expressed protein has the potential to be cross-reactive with existing known allergens. For any protein that would be newly expressed in a GM crop, the bioinformatic assessment compares the identity and position of each amino acid in the newly expressed protein with the identity and position of each amino acid in a database of approximately 2,000 known allergens. Therefore, using as an example a new protein that is 200 amino acids in length, this bioinformatics assessment results in approximately 41,000,000 comparisons with the allergen database. The net result of these exhaustive bioinformatic assessments for each newly introduced protein is that all commercialized GM crops have proteins that have been shown to have no meaningful similarity to known allergens. In more than 20 years, only 1 case has been documented in which a protein intended for a GM crop was prevented from being commercialized because of allergenicity concerns. This case was for a GM soybean that was to express a protein from Brazil nut (*Bertholletia excelsa*) that was discovered to be a known allergen. The studies used sera from patients allergic to Brazil nuts that were cross-reactive to the protein intended to be produced in the GM soybeans.²⁶ Because of this study, the developers of this GM soybean stopped work and did not submit the product for regulatory review for commercialization. This reflects the seed industry's commitment to commercializing only GM crops that are as safe as conventionally developed crops.

Abundance of protein in GM crop

There are a few key features of proteins that are shared by many food allergens. One feature is that allergenic proteins are typically expressed at high concentrations in the food source.^{27,28} For example, the allergenic proteins Ara h 1, Pru p 3 and Gly m 5 are present in 1,000 to 10,000 ppm in peanut, peach, and soybean respectively.^{27,28} By comparison, the proteins expressed in the grain of GM crops are typically at concentrations of 0.1 to 100 ppm orders of magnitude lower than sensitizing allergens.²⁹ Despite the low level of GM expression in crops and low-level human exposure, many studies have been performed to evaluate the allergenic potential of novel proteins in individuals with allergy. These studies have found no evidence that individuals with atopy have developed IgE to these proteins.^{30–33}

Protein digestibility

Another feature of proteins that increases the likelihood of eliciting an allergic reaction is resistance to digestion by proteolytic enzymes of the gastrointestinal tract.^{34–36} Intuitively, most dietary proteins are rapidly digested by pepsin and other gastrointestinal proteases, limiting exposure of the gut immune system to sufficient intact peptides to elicit allergic reactions. However, some studies have shown that the correlation between degradation and loss of allergenic potential is not absolute.^{37,38} Nonetheless, Codex guidelines that most regulatory authorities follow require data on the susceptibility of a newly introduced protein to pepsin digestion as part of the overall weight of evidence to assess the safety of the protein.

Application of GM Organisms in the Global Food Marketplace

Genetically modified crops were first introduced to the market in 1996. In 2014, more than 18 million farmers from 28 countries grew GM crops. The adoption of these products has not only increased yield but also had a positive environmental impact by decreasing pesticide use, decreasing soil erosion from tillage, and lowering farm-related carbon emissions.¹⁰

Of the 9 GM crops grown commercially in the United States, 7 are commodity crops (corn, soybean, cotton, canola, sugar beet, and alfalfa) that are predominantly consumed by animals.³ Three (potato, papaya, and sweetcorn) are consumed directly by humans. The processed fractions from commodity crops such as oil, sugar, and starches have no residual protein products from GM crops.

Part 2

Relation Between GM Organisms and Allergy—A Systematic Review

The first part of this review detailed the history of GM product use and the immunology behind the mechanisms used to achieve genetic modification. This second part of the review investigates 2 fundamental questions often inquired about the use of GM products in our society:

1. Are GM products more allergenic than their conventional counterparts?
2. Is the use of GM products, compared with their conventional counterparts, associated with the development of allergic disease or a predicted risk of development of allergic disease?

To answer these questions, we undertook a systematic review of the literature.

Methods

With the assistance of a research librarian (University of Colorado—Denver School of Medicine Health Sciences Library), we conducted a literature search of multiple online databases,

supplemented with manual searches for grey literature and searches of allergy journals to ensure no additional potential references were missed. The search strategy is detailed in the online supplement. The literature search initially focused on human studies involving GM products. However, after a precursory pilot search and in consultation with the research librarian, 2 of the authors agreed to expand the focus to include animal model studies as broadly as possible. This expanded strategy identified 6,467 citations (Medline, n = 2,846; Embase, n = 2,330; Web of Science, n = 1,277; Cochrane Reviews, n = 14; plus an additional 6 pieces of gray literature not included in the citation total), which netted 4,399 citations once duplicates were removed.

These 4,399 references were loaded into Covidence (Melbourne, Victoria, Australia), where online review of citations was completed by the 2 authors of this section (M.J.G. and D.M.F.). As part of an a priori decision for disagreements regarding citation inclusion, each case was further discussed by these authors, with unanimous consensus necessary for definitive inclusion or exclusion. The final group of articles for full-text extraction were reviewed for evidence synthesis, identifying 104 studies, of which an additional 21 were excluded, leading to 83 studies included in the final analysis (Figs 1 and 2). Monsanto employees, who authored the first part of this review, were not involved with the systematic review, had no access to the literature search, analysis, or findings, and never reviewed this portion of the report. This partition was self-imposed to deliberately maintain maximal separation and avoid any potential input into the findings of this section of the review.

Results

In reference to the first query (“Are GM products more allergenic than their conventional counterparts?”), we identified 83 studies addressing this question: 23 studies of GM corn,^{32,33,39–59} 6 studies of GM wheat,^{60–65} 12 studies of GM rice,^{66–77} 14 studies of GM soy,^{26,57,78–88} 5 studies of GM peanut,^{89–93} 1 study of GM milk,⁹⁴ 16 studies of other GM products (apple, kale, pea, broccoli, tomato, salmon, mustard, potato),^{95–110} and 6 studies involving specific molecules and proteins used in genetic modification.^{111–116} No randomized controlled trials (RCTs) conducted in humans or in animals were identified in the literature search. Thirty-four human studies were identified, 32 of which involved human serum used for IgE binding and inhibition studies. We identified only 2 studies (1 observational and 1 quasi-experimental) that involved actual ingestion of a GM product.^{26,31–33,48,56–58,60–63,69,70,73,78–80,83,84,90,91,93,96,98,103–105,107–110,112} Forty-nine animal model studies were identified, most of which were controlled.^{39–47,49–51,53–55,64–68,71,72,74–77,82,84–88,92,94,95,97,99–102,106,111,113,114,117,118} These animal studies were conducted in rat or mouse models and involved ingestion of a GM product and assessment of various safety and toxicity parameters, including measurement of serologic allergic or immunologic markers.

Studies demonstrating evidence of harm

No animal or human study was identified that demonstrated evidence that a GM food item was more allergenic than its conventional counterpart. No studies were identified that demonstrated that direct consumption of a GM food was associated with an increased rate of clinical allergy (eg, allergy being defined as typical signs or symptoms of IgE-mediated mast cell reactivity in human or animal models) compared with its conventional counterpart. Of the 83 studies identified, only 3 noted increased sensitization to the GM product. Two of these studies were from animal models demonstrating an increase in the GM serum-specific IgE and increased serum eosinophil counts and T-helper cell type 2 cytokines with exposure to GM product (GM corn) compared with its conventional counterpart.

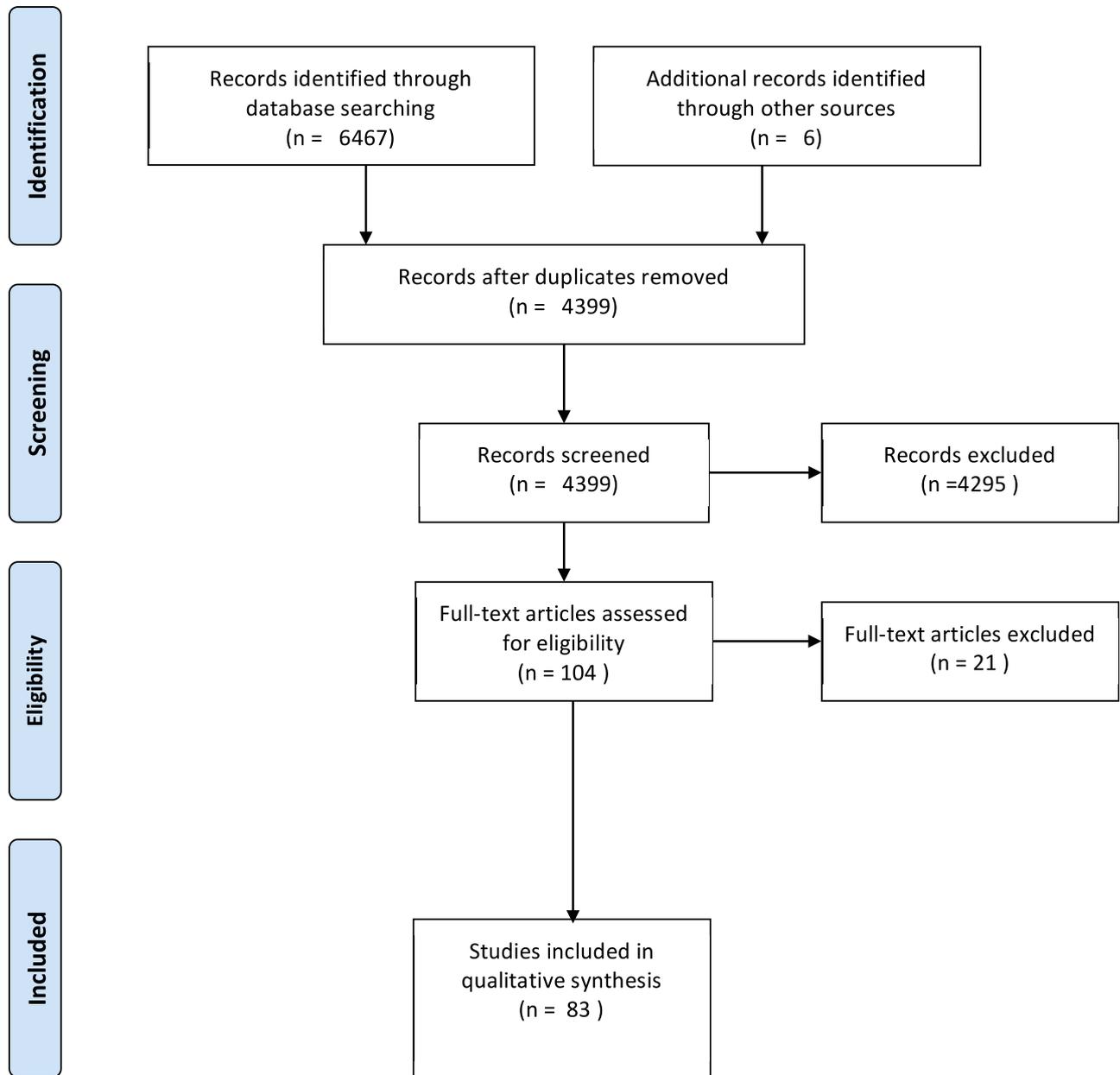


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of literature search.

However, neither study demonstrated that these increased markers resulted in any clinical allergy in the mouse models.^{43,44} The third study identified was a case series describing sensitization in subjects with known Brazil nut allergy (by skin testing, serum IgE testing, and western blotting) to GM soy through cross-recognition of a 2S albumin Brazil nut protein that had been genetically engineered into the soybeans to increase their nutritional value. However, none of these subjects with allergy to Brazil nut were challenged to the GM soy to demonstrate whether the sensitization had any clinical significance, although the investigators concluded that this demonstrated the potential for inadvertent allergen transfer through genetic modification.²⁶

Studies demonstrating no harm or potential benefit

Eighty studies were identified that demonstrated GM products were discretely nonallergenic or were not more allergenic than

their conventional counterparts.^{22,30–33,39–42,45–116} These included 47 animal studies and 33 human subject studies. Of the human studies, 31 involved use of human sera from subjects with known allergy to that food for detection of sensitization (or skin testing for similar detection), but only 2 involved direct human ingestion of a GM product. The first study was a case report of a double-blinded, placebo-controlled, food challenge to Starlink GM corn in an individual reporting multiple past reactions attributable to products containing Starlink corn but who demonstrated no reaction to this corn during challenge.⁵⁸ The second study was a trial demonstrating weaker symptoms in subjects allergic to apple who ingested a GM Elstar apple with decreased Mal d 1.⁹⁶ Eight studies were identified that noted that GM products demonstrated hypoallergenic properties compared with their conventional counterpart. These included 2 studies of apples engineered to have weaker Mal d 1 expression, which showed decreased apple sensitization and decreased symptoms after ingestion as measured on a visual

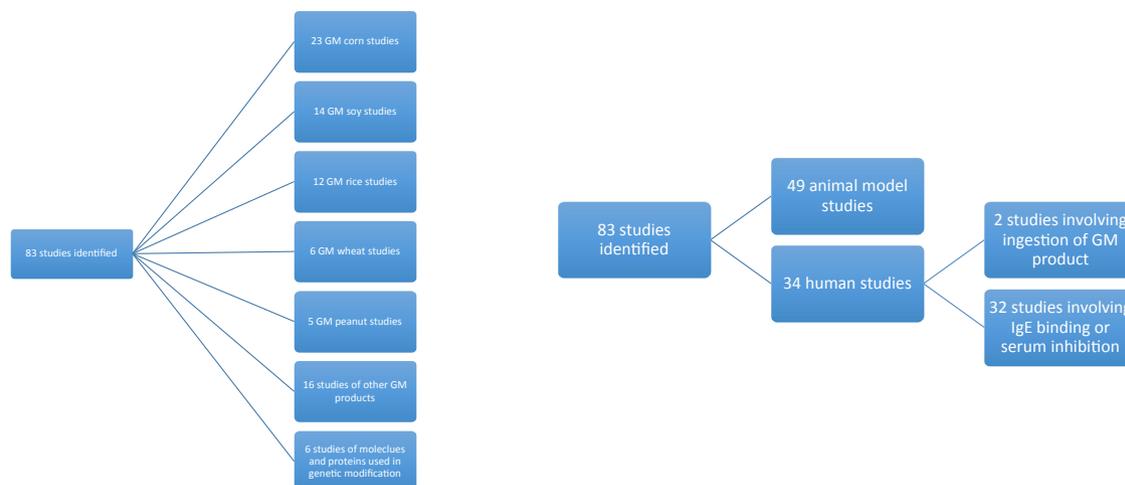


Figure 2. Breakdown of articles included in the systematic review.

analog scale compared with conventional apples.^{96,110} In addition, 2 studies of GM peanut,^{95,96} 2 of rice,^{69,72} and single studies of GM egg and tomato showed weaker IgE binding to the GM product compared with the conventional product.^{108,110}

In reference to the second query (“Is the use of GMO products, compared with conventional counterparts, associated with the development of allergic disease or a risk of development of allergic disease?”), our search did not identify any data from controlled studies of any type (RCT or controlled trial) that addressed this question. In 2016, the National Academy of Sciences (NAS) published a comprehensive report on genetically engineered crops, which noted that the reported increased prevalence of food allergy (and celiac disease) during the past couple of decades in the United States started before GM food products became available in 1996, and the same increase in food allergies within this timeframe also was noted in the United Kingdom, although GM food products are not common in that country.³ The NAS report concluded, “The committee did not find a relationship between consumption of GE foods and the increase in prevalence of food allergies.”³ Thus, because no controlled studies were identified, this question could not be directly answered, and no data currently exist to confirm or refute this potential hypothesis of query 2.

Meta-analysis

Because of the primarily animal model data with limited consistency between experimental design, animal model used, and outcome assessed, no RCTs identified, and limited human data involving direct consumption of GM product, no attempt at pooling data and performing meta-analysis was made.

Discussion

Use of GM food products remains an accepted, although possibly controversial, practice. There is a limited number of GM food products approved for human consumption, but use of GM food products as animal feed is more widespread.³ This systematic review evaluated whether GM products are associated with a risk of causing food allergy, and whether use of GM food products influenced the risk of developing food allergies. We identified only 83 relevant articles of approximately 4,400 citations, which included no RCT or placebo-controlled human studies involving consumption of GM products. In short, we found that (1) GM food products were discretely not allergenic or were not more allergenic than their conventional counterparts and (2) there are no controlled studies providing data that confirm or refute that

consumption of GM food products increases the risk of developing allergy, with a recent NAS report concluding that consumption of GM foods is not related to the increase in the prevalence of food allergies.³

Focusing on our first question, the human studies that were identified were primarily limited to the use of well-characterized sera of patients with a known food allergy to a conventional product, where that serum was tested for IgE binding properties against the GM product. According to the World Health Organization, this is a preferred strategy to test for baseline differences in allergenicity, dating back to the mid-1990s.^{12,13} In these situations, there was no evidence to support that GM products are more allergenic than their conventional counterparts; in fact, 7 of these studies suggested that the IgE binding properties of the GM products were actually weaker than those of their conventional counterparts, suggesting that the GM products in those studies could be viewed as potentially hypoallergenic.^{69,73,91,93,96,103,109,110} We did identify 2 studies involving human ingestion of GM products, but neither demonstrated that ingestion of the GM food was associated with allergy (to Starlink GM corn, disproven by double-blinded, placebo-controlled, food challenge; or to apple with decreased Mal d 1, which noted significantly less symptom development at ingestion by patients allergic to apple).^{58,96}

Regarding Starlink corn, this product was approved for animal use in the late 1990s, but then somehow made its way into the human food chain and was detected in some products. Subsequently, approximately 28 case reports were fielded by the Centers for Disease Control and Prevention and deemed suspicious for “apparent allergic reactions” to Starlink corn-containing products. However, serologic testing failed to show relevant IgE binding of Starlink proteins in patients with known corn sensitization. Furthermore, in the only objective study of human ingestion of this product, a patient with alleged allergy to Starlink corn did not react to the corn during a 3-day inpatient double-blinded, placebo-controlled, food challenge. Starlink corn’s premarket internal safety testing of the GM Cry9Ab protein noted slow digestibility in simulated digestion studies (another method approved by the World Health Organization for assessing allergenicity), leading investigators to theorize the peptides could remain large enough for immune system recognition but there were no data to substantiate that it is an actual allergen.^{58,117,118} Therefore, as a sensitivity analysis, inclusion of these data on Starlink corn would not alter our conclusion to question 1.

For the second query, we could not identify any controlled data that addressed the effect of consumption of GM products and the risk of developing food allergy.

There was an abundance of animal model studies supporting the safety of GM food products. Animal models, in particular rat and mouse models, are well-accepted surrogates for the study of allergic disease in humans. However, because no human randomized, placebo-controlled, or controlled studies were identified, we did not attempt meta-analysis and instead present a systematic review of the findings. There would have been difficulty in pooling animal model data given the heterogeneous study design, model choice, and methodology. Moreover, because the questions of greatest concern were related to the risk of food allergy in humans from GM products, we did not attempt meta-analysis of these data because of questionable relevance and generalizability of such pooled animal data to humans. We consider these limitations of our study.

Conclusion

Based on the data to date identified in this systematic review, we conclude that, in reference to the first query, GM products do not appear more allergenic than their conventional counterparts as determined by IgE binding studies in well-characterized sera from humans with allergy and animal models, case series of direct provocation and ingestion, and simulated digestion studies. These are methods approved by the World Health Organization for determining allergenicity of GM products.¹³ We did identify limited evidence that genetic modification, in some instances, resulted in the product having decreased IgE binding capacity in subjects with allergy compared with its conventional counterpart, which could indicate hypo-allergenicity, although this concept requires more robust study. It is important to emphasize that known allergens to an individual, be it in a GM form or conventional form, will still be allergenic in that individual and it should be avoided. This review also highlights that there is no evidence that eating GM products in individuals who are not allergic to conventional forms of those items would result in allergy or increase the risk of developing an allergy to that item.

For the second query, there were no animal or human studies identified that evaluated the effect of the consumption of GM products and the overall risk of developing a food allergy or other allergic disease. Thus, given no controlled studies and no proven medical evidence to support or refute an association between use of GM products and the development or risk of developing food allergies, no data outside the NAS report conclusion are available to evaluate this hypothesis.³ This would represent a knowledge gap where future study could be highly informative. In conclusion, although individuals with allergy should avoid conventional and GM forms of that particular food, GM foods do not appear to be more allergenic than their conventional counterparts, and no data exist that consumption of GM proteins causes allergy to develop to that particular food in individuals who are not allergic at baseline.

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Supplementary Data

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Supplementary Data

Search Summary Used by the Research Librarian for the Systematic Review Portion

Database	Genetically modified organism	Food allergy
Text words	“Genetically Modified Organism” OR “Genetically Modified Organisms” OR GMO* OR “Genetically Engineered Organism” OR “Genetically Engineered Organisms” OR “Transgenic Organism” OR “Transgenic Organisms” OR “Genetically Modified Plant” OR “Genetically Modified Plants” OR “Genetically Engineered Plant” OR “Genetically Engineered Plants” OR “Transgenic Plant” OR “Transgenic Plants” OR “Genetically Modified Food” OR “Genetically Modified Foods” OR “Genetically Engineered foods” OR “Genetically Engineered food” OR “Genetically Modified Animal” OR “Genetically Modified Animals” OR “Genetically Engineered Animal” OR “Genetically Engineered Animals” OR “Transgenic Animal” OR “Transgenic Animals” OR “Transgenic Founder Animal” OR “Transgenic Founder Animals” OR “Genetically Modified crop” OR “Genetically Modified crops” OR “Genetically engineered crop” OR “Genetically engineered crops” OR (“genetically modified” OR “genetic modification” OR “genetically engineered” OR “genetic engineering” OR transgenic) AND (food* OR organism* OR plant* OR animal* OR crop* OR soy* OR wheat OR seed* OR grain*)	“food allergy” OR “food allergies” OR “food hypersensitivity” OR “food hypersensitivities” OR ((Allerg* OR hypersensitiv* OR sensitiz* OR sensitiz* OR anaphyla*) AND (food* OR feed* OR diet* OR nutrit* OR nutrient* OR edible OR consume OR consumed OR consumption OR oral* OR human* OR patient* OR subject*))
Subject headings Medline	“Organisms, Genetically Modified”[Mesh] OR “Food, Genetically Modified”[Mesh]	“Food Hypersensitivity”[Mesh] OR ((“Hypersensitivity”[Mesh:NoExp] OR “Hypersensitivity, Delayed”[Mesh] OR “Hypersensitivity, Immediate”[Mesh] OR “Allergens”[Mesh] OR “Anaphylaxis”[Mesh]) AND (“Food”[Mesh] OR “Food Safety”[Mesh] OR “Diet”[Mesh] OR “Nutritional Sciences”[Mesh] OR “Humans”[Mesh] OR “Research Subjects”[Mesh] OR “Patients”[Mesh]))
Embase	'transgenic organism'/exp OR 'genetically modified food'/exp	'food allergy'/exp OR 'food allergen'/exp OR (('hypersensitivity'/exp OR 'allergen'/exp OR 'anaphylaxis'/exp) AND ('food'/exp OR 'food safety'/exp OR 'diet'/exp OR 'nutritional science'/exp OR 'human'/exp OR 'research subject'/exp OR 'patient'/exp))
Medline (through PubMed); January 25, 2017; 2,846 results	(“Genetically Modified Organism”[tw] OR “Genetically Modified Organisms”[tw] OR GMO*[tw] OR “Genetically Engineered Organism”[tw] OR “Genetically Engineered Organisms”[tw] OR “Transgenic Organism”[tw] OR “Transgenic Organisms”[tw] OR “Genetically Modified Plant”[tw] OR “Genetically Modified Plants”[tw] OR “Genetically Engineered Plant”[tw] OR “Genetically Engineered Plants”[tw] OR “Transgenic Plant”[tw] OR “Transgenic Plants”[tw] OR “Genetically Modified Food”[tw] OR “Genetically Modified Foods”[tw] OR “Genetically Engineered foods”[tw] OR “Genetically Engineered food”[tw] OR “Genetically Modified Animal”[tw] OR “Genetically Modified Animals”[tw] OR “Genetically Engineered Animal”[tw] OR “Genetically Engineered Animals”[tw] OR “Transgenic Animal”[tw] OR “Transgenic Animals”[tw] OR “Transgenic Founder Animal”[tw] OR “Transgenic Founder Animals”[tw] OR “Genetically Modified crop”[tw] OR “Genetically Modified crops”[tw] OR “Genetically engineered crop”[tw] OR “Genetically engineered crops”[tw] OR (“genetically modified”[tw] OR “genetic modification”[tw] OR “genetically engineered”[tw] OR “genetic engineering”[tw] OR transgenic[tw]) AND (food*[tw] OR organism*[tw] OR plant*[tw] OR animal*[tw] OR crop*[tw] OR soy*[tw] OR wheat[tw] OR seed*[tw] OR grain*[tw])) OR “Organisms, Genetically Modified”[Mesh] OR “Food, Genetically Modified”[Mesh]) AND (“food allergy”[tw] OR “food allergies”[tw] OR “food hypersensitivity”[tw] OR “food hypersensitivities”[tw] OR ((Allerg*[tw] OR hypersensitiv*[tw] OR sensitiz*[tw] OR sensitiz*[tw] OR anaphyla*[tw]) AND (food*[tw] OR feed*[tw] OR diet[tw] OR diets[tw] OR dietet*[tw] OR dieter*[tw] OR nutrit*[tw] OR nutrient*[tw] OR edible[tw] OR consume[tw] OR consumed[tw] OR consumption[tw] OR oral*[tw] OR human*[tw] OR patient[tw] OR patients[tw] OR subject*[tw])) OR “Food Hypersensitivity”[Mesh] OR ((“Hypersensitivity”[Mesh:NoExp] OR “Hypersensitivity, Delayed”[Mesh] OR “Hypersensitivity, Immediate”[Mesh] OR “Allergens”[Mesh] OR “Anaphylaxis”[Mesh]) AND (“Food”[Mesh] OR “Food Safety”[Mesh] OR “Diet”[Mesh] OR “Nutritional Sciences”[Mesh] OR “Humans”[Mesh] OR “Research Subjects”[Mesh] OR “Patients”[Mesh]))))	

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(continued)

Database	Genetically modified organism	Food allergy	
Embase (through Embase.com); January 27, 2017; 2,330 results	('Genetically Modified Organism':ab,ti OR 'Genetically Modified Organisms':ab,ti OR GMO*:ab,ti OR 'Genetically Engineered Organism':ab,ti OR 'Genetically Engineered Organisms':ab,ti OR 'Transgenic Organism':ab,ti OR 'Transgenic Organisms':ab,ti OR 'Genetically Modified Plant':ab,ti OR 'Genetically Modified Plants':ab,ti OR 'Genetically Engineered Plant':ab,ti OR 'Genetically Engineered Plants':ab,ti OR 'Transgenic Plant':ab,ti OR 'Transgenic Plants':ab,ti OR 'Genetically Modified Food':ab,ti OR 'Genetically Modified Foods':ab,ti OR 'Genetically Engineered foods':ab,ti OR 'Genetically Engineered food':ab,ti OR 'Genetically Modified Animal':ab,ti OR 'Genetically Modified Animals':ab,ti OR 'Genetically Engineered Animal':ab,ti OR 'Genetically Engineered Animals':ab,ti OR 'Transgenic Animal':ab,ti OR 'Transgenic Animals':ab,ti OR 'Transgenic Founder Animal':ab,ti OR 'Transgenic Founder Animals':ab,ti OR 'Genetically Modified crop':ab,ti OR 'Genetically Modified crops':ab,ti OR 'Genetically engineered crop':ab,ti OR 'Genetically engineered crops':ab,ti OR (('genetically modified':ab,ti OR 'genetic modification':ab,ti OR 'genetically engineered':ab,ti OR 'genetic engineering':ab,ti OR transgenic:ab,ti) AND (food*:ab,ti OR organism*:ab,ti OR plant*:ab,ti OR animal*:ab,ti OR crop*:ab,ti OR soy*:ab,ti OR wheat:ab,ti OR seed*:ab,ti OR grain*:ab,ti)) OR 'transgenic organism'/exp OR 'genetically modified food'/exp) AND ('food allergy':ab,ti OR 'food allergies':ab,ti OR 'food hypersensitivity':ab,ti OR 'food hypersensitivities':ab,ti OR ((Allerg*:ab,ti OR hypersensitiv*:ab,ti OR sensitiz*:ab,ti OR sensitis*:ab,ti OR anaphyla*:ab,ti) AND (food*:ab,ti OR feed*:ab,ti OR diet*:ab,ti OR nutrit*:ab,ti OR nutrient*:ab,ti OR edible:ab,ti OR consume:ab,ti OR consumed:ab,ti OR consumption:ab,ti OR oral*:ab,ti OR human*:ab,ti OR patient*:ab,ti OR subject*:ab,ti)) OR 'food allergy'/exp OR 'food allergen'/exp OR (('hypersensitivity'/exp OR 'allergen'/exp OR 'anaphylaxis'/exp) AND ('food'/exp OR 'food safety'/exp OR 'diet'/exp OR 'nutritional science'/exp OR 'human'/exp OR 'research subject'/exp OR 'patient'/exp))		
Web of Science (through Thomson Reuters, including Science Citation Index Expanded 1974–present and Social Sciences Citation Index 1974–present); January 26, 2017; 1,277 results	TS = ("Genetically Modified Organism" OR "Genetically Modified Organisms" OR GMO* OR "Genetically Engineered Organism" OR "Genetically Engineered Organisms" OR "Transgenic Organism" OR "Transgenic Organisms" OR "Genetically Modified Plant" OR "Genetically Modified Plants" OR "Genetically Engineered Plant" OR "Genetically Engineered Plants" OR "Transgenic Plant" OR "Transgenic Plants" OR "Genetically Modified Food" OR "Genetically Modified Foods" OR "Genetically Engineered foods" OR "Genetically Engineered food" OR "Genetically Modified Animal" OR "Genetically Modified Animals" OR "Genetically Engineered Animal" OR "Genetically Engineered Animals" OR "Transgenic Animal" OR "Transgenic Animals" OR "Transgenic Founder Animal" OR "Transgenic Founder Animals" OR "Genetically Modified crop" OR "Genetically Modified crops" OR "Genetically engineered crop" OR "Genetically engineered crops" OR (("genetically modified" OR "genetic modification" OR "genetically engineered" OR "genetic engineering" OR transgenic) AND (food* OR organism* OR plant* OR animal* OR crop* OR soy* OR wheat OR seed* OR grain*)) AND TS = ("food allergy" OR "food allergies" OR "food hypersensitivity" OR "food hypersensitivities" OR ((Allerg* OR hypersensitiv* OR sensitiz* OR sensitis* OR anaphyla*) AND (food* OR feed* OR diet* OR nutrit* OR nutrient* OR edible OR consume OR consumed OR consumption OR oral* OR human* OR patient* OR subject*))		
	ID	Search	Hits
Cochrane Library (through CochraneLibrary.com , including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, and NHS Economic Evaluation Database); January 26, 2017; 14 results	#1	("Genetically Modified Organism" or "Genetically Modified Organisms" or GMO* or "Genetically Engineered Organism" or "Genetically Engineered Organisms" or "Transgenic Organism" or "Transgenic Organisms" or "Genetically Modified Plant" or "Genetically Modified Plants" or "Genetically Engineered Plant" or "Genetically Engineered Plants" or "Transgenic Plant" or "Transgenic Plants" or "Genetically Modified Food" or "Genetically Modified Foods" or "Genetically Engineered foods" or "Genetically Engineered food" or "Genetically Modified Animal" or "Genetically Modified Animals" or "Genetically Engineered Animal" or "Genetically Engineered Animals" or "Transgenic Animal" or "Transgenic Animals" or "Transgenic Founder Animal" or "Transgenic Founder Animals" or "Genetically Modified crop" or "Genetically Modified crops" or "Genetically engineered crop" or "Genetically engineered crops" or (("genetically modified" or "genetic modification" or "genetically engineered" or "genetic engineering" or transgenic) and (food* or organism* or plant* or animal* or crop* or soy* or wheat or seed* or grain*)):ti,ab,kw	159
	#2	MeSH descriptor: [Organisms, Genetically Modified] explode all trees	20
	#3	MeSH descriptor: [Food, Genetically Modified] explode all trees	12
	#4	#1 or #2 or #3	159
	#5	("food allergy" or "food allergies" or "food hypersensitivity" or "food hypersensitivities" or ((Allerg* or hypersensitiv* or sensitiz* or sensitis* or anaphyla*) and (food* or feed* or diet* or nutrit* or nutrient* or edible or consume or consumed or consumption or oral* or human* or patient* or subject*)):ti,ab,kw	20,307
	#6	MeSH descriptor: [Food Hypersensitivity] explode all trees	676
	#7	#5 or #6	20,308
	#8	#4 and #7	14
Total			
Database			Results
Medline			2,846
Embase			2,330
Web of Science			1,277
Cochrane			14
Database subtotal			6,467
Additional records (grey literature)			6
Duplicates removed			2,074
Total (excluding duplicates)			4,399

Manual search

From Web of Science InCites Journal Citation Reports 2015 (SCIE and SSCI), top 4 journals in the allergy category, searched from 2013 to 2017

Journal of Allergy and Clinical Immunology—no additional articles identified

Allergy—no additional articles identified

Contact Dermatitis—no additional articles identified

Clinical and Experimental Allergy—no additional articles identified

Grey Literature

Food and Drug Administration

- [1] Guidance for industry: voluntary labeling indicating whether foods have or have not been derived from genetically engineered plants. <http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm059098.htm>. Accessed January 31, 2017.
- [2] Genetically engineered foods. Statement of James H. Maryanski, PhD (Biotechnology Coordinator, Center for Food Safety and

Applied Nutrition, Food and Drug Administration) before the Subcommittee on Basic Research, House Committee on Science, October 19, 1999. <http://www.fda.gov/newsevents/testimony/ucm115032.htm>. Accessed January 31, 2017.

- [3] Statement of policy—foods derived from new plant varieties. <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm>. Accessed January 31, 2017.
- [4] Questions & answers on food from genetically engineered plants. <http://www.fda.gov/food/ingredientspackaginglabeling/geplants/ucm346030.htm>. Accessed January 31, 2017.
- [5] FDA has determined that the AquAdvantage salmon is as safe to eat as non-GE salmon. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm472487.htm>. Accessed February 3, 2017.

Institute of Medicine

- [1] Safety of genetically engineered foods: approaches to assessing unintended health effects. <https://www.nap.edu/read/10977/chapter/1>. Accessed February 3, 2017.