How safe does transgenic food need to be?

Laura DeFrancesco

Disputes over how to assess a foodstuff's safety continue to play into public fears about transgenic crops.

Transgenic crops are the most highly regulated foods in the world. In recent years, there have been calls in the United States to relax some of the rules for their oversight. And yet controversies over the safety of transgenic food products continue to rumble, particularly in Europe, Africa and now further afield in the Far East. Despite the fact that numerous national and international scientific panels have concluded that food derived through transgenic approaches is as safe as food produced in other ways and that foodborne pathogens pose a much greater threat to human health[1], scare stories continue to appear in the media and questions continue to be asked about the adequacy of current regulatory systems to determine the safety of our food, transgenic or otherwise.

Why, after transgenic products have been in the human food chain for more than a decade without overt ill effects, do these doubts persist? And will it ever be possible to gather sufficient evidence to ameliorate the concerns of skeptics and the public at large that these products are as safe as any other foodstuff?

Different strokes

Regulators in the United States and the European Union (EU; Brussels) approach the issue of safeguarding the food supply in different ways. The US Food and Drug Administration (FDA) has a voluntary process that leaves the burden of ensuring the safety of new foods to the developers, under the notion of 'substantial equivalence': "if a new food is found to be substantially equivalent to an existing food, the food can be concluded to be as safe as the conventional food" (slightly edited for readability from ref. 2).

"There are no pre-market reviews of approvals required of foods. Instead, manufacturers or distributors bear the burden of ensuring that any finished food placed on the market meets the safety levels implicit in the definition of adulterated foods. FDA is authorized to seek sanctions against foods that do not adhere to these standards through seizure, injunction or criminal prosecution," writes Emily Marden of the University of British Columbia's Faculty of Law in Vancouver[3]. This holds for all new foods, whether transgenic or not.

Notwithstanding the absence of legal underpinnings, a *de facto* regulatory process (called a consultation) exists at the FDA, whereby companies submit information on new genetically modified foods destined for the market (**Supplementary Box 1**).

In contrast, since the European Council adopted Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms in 1990 (ref. 4), the EU has increasingly employed the precautionary principle, which requires developers to prove the safety of any new food that has "not hitherto been used for human consumption to a significant degree within the community" before it can be placed on the market. This includes transgenic products under the EU Directive 90/220/EEC covering plants and the Regulation (EC) 258/97, which relates to novel foods and food ingredients. "In Europe…you can't get a food on the market until it's met safety criteria," says Julian Kinderlerer, professor of law at the University of Cape Town, South Africa. In the United States, "foods are subject to generally-recognized-as-safe criteria," he adds. "The FDA can't stop something from going on the market; they have to go to court to get it off."

The assessment process

The United States has had a tripartite regulatory process for transgenic crops since 1986 when the Coordinated Framework for Regulation of Biotechnology was laid out (51 Fed. Reg. 23302, June 26, 1986)[5]. Depending on the exact nature of the change made to the crop, the US Department of Agriculture (USDA), the US Environmental Protection Agency (EPA) and/or the FDA has regulatory authority. The USDA, and the Animal and Plant Health Inspection Service within it, is responsible for regulating agricultural plant pests and noxious weeds under, among others, the Plant Protection Act and so looks at the environmental impact of transgenic crops; similarly the EPA is responsible for oversight of transgenic crops that contain pesticides within them under regulations for "plant-incorporated pesticides." But it is the FDA and its Center for Food Safety and Applied Nutrition that is responsible for oversight of the safety of food derived from transgenic crops destined for human consumption.

Genetically modified sweet corn seed has been part of the American diet since 1998 when Syngenta's insect-protected corn was approved. Monsanto started selling transgenic sweet corn three years later.

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Under the "adulterated food provisions" of the Federal Food, Drug, and Cosmetic Act[6], the FDA regulates such food using the principle of history of safe use: a substance may be considered to have a history of safe use as a food if it has been an ongoing part of the diet for several generations in a large genetically diverse human population.

Seed companies developing food ingredients submit a package of information on a transgenic product that includes the source of the gene, characterization of the insert and some compositional analysis of the new food. Tests are targeted to measure specific molecules or entities—plant toxins, anti-nutrients and allergens—to look for unintended up- or downregulation of critical molecules that might have occurred during the creation of the transgenic plant. Toxicology and allergenicity studies are typically conducted on the isolated proteins or molecules to be newly expressed in the plant, although often the material for testing is made by recombinant techniques in bacteria (and the resultant protein may have small differences in post-translational modifications from the version made in the transgenic plant), and rarely in the context of the plant. This is because of the difficulty of isolating the protein from a plant in sufficient quantities for testing and due to the complexity of feeding studies with whole foods. No animal or human feeding studies are mentioned in FDA's guidance document[7].

Since 2002, the EU has had a consultancy in place—the European Food Safety Authority (EFSA)—that specifically provides advice on risk assessment of foods, including transgenic crops. The process for evaluating transgenic crops is based largely on guidances set out by the United Nations' Food and Agriculture Organization (FAO; Rome), the Organization for Economic Cooperation and Development (Paris), the World Health Organization (WHO; Geneva) and the FAO/WHO Codex Alimentarius (reviewed in ref. 8). EFSA's guidance documents are more detailed than those of the FDA, but much is still left up to the developers of new foods as to the exact information they provide. Both the FDA and EFSA require similar kinds of information on the nature of the genetic insert and the plant. Whereas feeding studies are at least mentioned in EFSA guidances, they are not required. However, the EU recently issued a revised regulation requiring 90-day feeding studies; EFSA has always argued that it should be done only when deemed necessary, as has been discussed elsewhere[9].

Compositional analyses of 129 transgenic crops submitted to the FDA for marketing authority from 1995 to 2012 have all failed to detect any significant differences—or any believed to have biological relevance—between the engineered plant and its nonengineered counterpart or reference species according to an analysis of the literature conducted jointly by FDA and Dow AgroScience scientists[10]. Included in the compositional analysis are proximates (crude measures of protein, fat, ash and fiber), amino acids, fatty acids, calcium and phosphate. Were significant differences from natural variation of an isogenic to be detected, they would become the focus of further investigation.

For all transgenic events commercialized so far, the concentration of the newly introduced protein in the context of a whole plant (and the consumable parts derived from it) has been so low that it has been considered not to pose a risk. Thus, the position of industry and US and EU regulators is that a combination of targeted compositional analysis plus an event's phenotypic and agronomic behavior provides everything needed to establish the safety of a transgenic crop.

Allergenicity

Another food safety concern arising from an alteration in food composition is the possibility of increased allergenicity. Several kinds of studies address this. One type compares sequences from the new food to those of known plant allergens, whose sequences are available in various public protein databases, including one dedicated to protein allergens (http://www.allergenonline.com/). The generally accepted standard for flagging a protein as a potential allergen is homology greater than 35% over a stretch of 80 amino acids or a stretch of identical amino acids, between 6 and 8 depending on the guidance. These are conservative metrics, according to Richard Goodman, at the University of Nebraska's Food Allergy Research and Resource Program in Lincoln. "It would capture marginal sequences that are unlikely to pose a risk of cross-reactivity," he says. Work from Goodman's laboratory and elsewhere has shown that the eight amino-acid match, in particular, is not predictive of allergenicity (ref. 11 and unpublished work from the Goodman laboratory). Goodman says that as a consequence this is being used less by food developers and regulatory agencies. In fact, EFSA has dropped the eight amino-acid matching entirely in its most recent guidance document[12], and the EU is expected to adopt this guidance this year, Goodman says.

Once regions of homology are found, various *in vitro* tests of allergenicity can be done (testing serum from allergic individuals, basophil release assay), although such tests on their own are not definitive. How do regulatory agencies deal with this uncertainty?

Tests such as these are rarely relied upon, according to Goodman, as proteins with high identity matches would be dropped. Instead, regulators rely on a "weight of evidence" approach, which means you look at the information in aggregate and make some kind of determination as to the likelihood of problems occurring.

A second approach to determining allergenicity of a protein is to measure its stability in low pH conditions and/or in the presence of pepsin. Considerable effort has been put in by FAO and WHO to standardize these tests[13], but the exact conditions are determined by the developer of the plant, not the regulatory agency.

A frequently cited example from the 1990s generally comes up when discussing the ability to detect whether a newly created food is allergenic. A methionine-rich protein (2S albumin) from the Brazil nut was inserted into soybean by scientists at the University of Nebraska and the agbiotech company Pioneer Hybrid of Johnston, Iowa, to improve the nutritional balance of soy for use as poultry feed (and reduce the need for costly feed supplements). However, the engineered soy plant was found to cause skin reactions in people allergic to Brazil nuts, which confirmed that an allergen can be transferred from one plant to another. This finding not only eliminated the plant from the product pipeline before any harm was done—a testament to the ability of the available tests to detect introduced allergens—but also enabled researchers to identify the source of the allergy in Brazil nuts, which, before this, was unknown[14].

In this case, a protein was taken from a plant known to be allergenic in humans, for which human immune sera exist for testing purposes. Nowadays, such transfers are less likely to be done, which makes testing for allergenicity a challenge, according to Hugh Sampson, professor of pediatrics, allergy and immunology at Mt. Sinai Hospital in New York, who in 2001 served as an advisor to the EPA on allergenicity studies of the Cry9c protein, present in Starlink corn. "If you bring a novel protein in, where we don't know if people are allergic, we can't really screen for what we don't know," he says.

Whereas the incidence of food allergies are on the rise (CDC reports the incidence of food allergies in children under 18 rose from 3.4% to 5.1% between 1997 and 2011), the cause of the rise, as well as whether it is linked to new allergens or existing ones, is not clear. However, the possibility of introducing a food allergen exists in all new foods (e.g., kiwi fruit, introduced into the American diet rather recently, turned out to be allergenic), and is not limited to genetically modified foods.

Neither allergenicity or toxicity has been a problem, according to Alan McHughen,

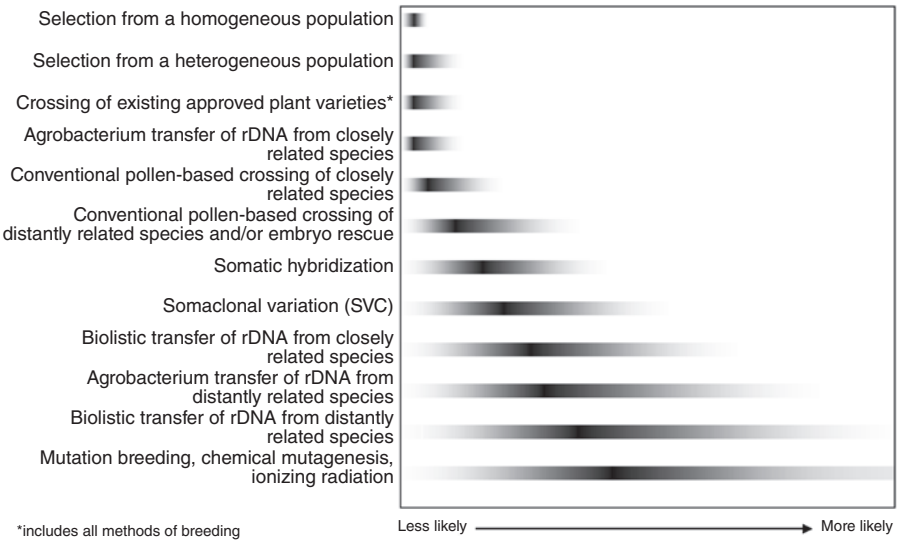

Figure 1 The NAS committee on the safety of genetically engineered food expressed the likelihood of unintended changes as a continuum with gene transfer more likely than all other modification techniques other than mutagenesis.

cooperative extension specialist in biotechnology for sustainable agriculture at the University of California, Riverside, who was a member of a panel convened in 2004 by the National Research Council of the US National Academy of Sciences to assess safety testing of transgenic foods. "We say in [the resulting report] that we were unable to identify any actual incidence of harm from the consumption of genetically engineered foods, and during our public input session, we requested people to bring us evidence. None of those were borne out"[15]. However, this group did find the potential for unintended changes to be higher for genetically modified crops than most other modification techniques (**Fig. 1**).

Points of contention

The above processes represent some of the current best practices used to assess the safety of foods. However, there are those who feel oversight is still too lax. For example, the Center for Food Safety (CFS; Washington, DC), whose position on GMOs is that they should not be released unless and until they have been proven safe for human health and the environment, has criticized the voluntary system used by US regulators, going so far as to say companies currently "game" the system by testing a wide diversity of reference varieties so that differences in composition due to a transgenic trait are masked. When statistically significant differences are seen in compositional analyses, even dramatic ones that fall outside the range of reference varieties, often they are discounted as not being biologically relevant, according to the center's science policy analyst Bill Freese.

For example, in a review of the documents submitted to the FDA by Monsanto for its Vistive Gold soybean oil and the plant from which it is derived (MON87705, a transgenic hybrid with high oleic and low linoleic acid levels), Freese notes that through targeted compositional testing the company found differences in 9 fatty acids (out of 17 that they could measure), that were unintended, in comparison to the conventional control as well as a number of commercial varieties. Whereas the changes observed pose no hazard, their presence, Freese says, indicates a need for further study, as other potentially hazardous changes, not captured by targeted analysis, might have occurred. To this criticism, a Monsanto spokesperson replies, "CFS refers to many significant differences yet seems to confuse statistical significance with unintended effects or biological relevance. The lack of meaningful differences in the composition of MON87705 seed and processed fractions does not form the basis for further non-targeted studies."

Another critique is that only a few targeted components of a food (amino acids, fatty acids, fiber, mineral and moisture) are analyzed in current assessments. With the availability of transcriptomics, proteomics and metabolomics, broader, systematic analytical testing of a new product could be carried out. Several independent groups that have looked at risk assessment of transgenic foods have concluded that better analytical methods are needed. These include an EFSA GMO Working Group on Animal Feeding Studies empaneled in 2008 (ref. 16), and the 2004 NRC panel. So far, omics technologies have not been integrated in the testing despite calls since 2001 to do so[17].

In an EU-sponsored project called SafeFoods, researchers conducted a series of studies over the past few years to try to answer the question of how best to apply omics technologies to plants. They looked not just at transgenic crops but crops grown under different growing conditions. Esther Kok, who was a member of the team, says that transcriptomics was the most informative, whereas the other types of omics data provided only partial information, representing as little as 10% of the 'ome' being analyzed[18].

For their part, food companies stand behind their analysis. Barbara Mazur, Vice President, Research Strategy for DuPont Pioneer, Johnston, Iowa, says, "Two decades of comprehensive study have demonstrated the safety of plant biotechnology. Analytical science is always producing more sensitive and new instrumentation, but it's not always appropriate to apply. There has to be a risk/benefit approach.

As transgenic foods already undergo extensively more testing than conventional food, the question becomes when is enough testing enough? Certainly, the amount of testing should be commensurate with the nature and magnitude of the risk associated with the new food. And according to Bruce Chassy, of the University of Illinois' Department of Food Science and Human Nutrition in Urbana-Champaign, "there's significant science behind [saying] that if you look at different varieties of the same crop, the transcriptomes are all different, metabolomes are all different, the proteomes are all different. If you look at a [transgenic] plant from one of those varieties, the proteome, transcriptome and metabolome are more like the parent variety than are other varieties of the same crop." Thus, one might invest considerable time and money into such analyses, without getting closer to answering whether a food is safe.

How long is long enough?

It is generally accepted among regulators and food developers that 90-day feeding studies with rodents are sufficient to detect chronic, long-term problems that might occur when humans are exposed to a new foodstuff. This notion appears to have come from studies carried out in the 1990s by the US National Toxicology Program in which it was asked whether toxicological effects of some 40 substances can be identified in subchronic, short-term feeding studies[19]. According to EFSA's own description of this work, 70% of findings (i.e., events connoting toxicity) at two years were predicted by a three-month subchronic study[8].

Last September, Gilles-Eric Séralini and his colleagues published a report of a study (**Box 1**),

whose aim was to follow rats fed corn engineered for resistance to the Roundup Ready herbicide glyphosate for much longer than 90 days—in this case, two years[20]. According to Séralini, such long-term feeding experiments are needed because too few studies attempt to model long-term chronic effects from eating transgenic crops. Although numerous problems have since been identified in the experiment's design and with its statistical rigor, problems that undercut the plausibility of Séralini's results and conclusions, a larger question remains as to whether the existing short-term animal feeding studies (90 days or less) are a reasonable surrogate for assessing the potential long-term, chronic effects of a new food, whether or not it's transgenic, on human beings. In December, the EU called for a two-year carcinogenicity study. So far, the GRACE project (GMO Risk Assessment and Communication of Evidence), a EU FP7-supported program, has performed only 90-day feeding studies with a year-long one in their plans.

Even some of those who back continued use of 90-day feeding studies feel that such studies are a compromise. Martijn Katan, emeritus professor of nutrition at Amsterdam's VU University says, "Few toxicologists ever stop to think whether such animal tests really predict the effect in humans, because if we start to doubt this dogma, the whole system collapses."

Indeed, in the peer-reviewed literature, opinions are conflicting as to the necessity of longer-term feeding studies. For example, two recent reviews on the safety of some transgenic crops came to different conclusions as to what the available evidence shows. A meta-analysis of 24 feeding studies done by an international team of toxicologists and biologists led by geneticist Agnes Ricroch of the University of Paris concluded that the long-term studies did not add any information to the safety assessment of individual crops[21].

In contrast, Jose L. Domingo, a toxicologist at the Universitat Rovira i Virgili in Reus, Spain, who has been probing the literature on the safety of transgenic crops since 2000, finds that the numbers of studies showing no harm are now roughly equal to those showing harm based on a selection of 30 articles [22].

Nature Biotechnology's own survey of the peer-reviewed literature of feeding studies designed to assess the effects of GMOs on human health reveals that, whereas there is a large number of feeding studies (over 100 in an nonexhaustive literature search; see **Supplementary Table 1**), 65% of the studies (70/108) are short-term feeding studies (90 days or less). For the most part, the literature is inconsistent in terms of the kinds of tests

Box 1 Publish and be damned

Many members of the plant research community were incensed that the Séralini study, which contained several key experimental design and statistical flaws, was published in the reputable peer-reviewed journal *Food and Chemical Toxicity*, which is considered the journal of record for these kinds of studies. Séralini's imposition of a nondisclosure agreement on journalists requesting embargoed copies of the manuscript (purportedly an attempt simply to maximize publicity of his accompanying documentary and book that was launching at the same time) was also widely regarded as an attack on journalistic freedom, preventing the scientific community from providing journalists with comment that could have set the study's extraordinary results and conclusions in their proper context. The onslaught of invective from researchers following publication was swift and fierce. The journal printed 13 letters (some with dozens of signatories), castigating the editors and the authors of the study; only one was printed in support (although websites exist with dozens of letters in support, some of which were sent to the journal, but apparently not published). To date, the response from the journal's editor has been to publish a statement in which he stands by their procedures for peer review.

Putting the specifics of the Séralini case aside, the debacle highlights how a media circus surrounding a flawed paper can have long-term negative implications for public perception. Public disquiet spurred by scare stories on transgenic food can be difficult to correct, despite subsequent attempts to correct the record and counter initial misinformation.

Currently, there is no widespread mechanism for journals to quickly correct the publication record. Typically, several weeks to months may elapse as journal editors field comments from their communities and prepare worthy comments for posting online or in print. A notorious *Science* paper on arsenic-based life, for example, made quite a stir both in the scientific and popular press. Although doubts were expressed from the start, five months elapsed before the journal took action; in this case, the journal published papers explaining how so-called arsenic life could be an artifact (i.e., contamination of trace amounts of phosphorous in the media), without going so far as to retract the article.

The Committee on Publication Ethics retraction guidelines state that journal editors should consider retracting a paper if they have clear evidence that the findings are unreliable, either as a result of misconduct (e.g., data fabrication) or honest error (e.g., miscalculation or experimental error). Ivan Oransky, co-founder of the website *Retraction Watch* says, "This is a question for all people who are calling for retraction. Is this how you would handle a similarly flawed paper in your own field in your own journal, and based on the behavior we've seen and the comments we get on *Retraction Watch*, the answer is no."

With the advent of social media, the potential for quick airing of reactions—positive or negative—to controversial findings exists. At least one publisher, the Public Library of Science, provides links from papers to blog posts and tweets, regardless of the content. In terms of the online commenting on articles on the journal website, Theodora Bloom, editorial director at *PLOS Biology*, finds it of little use. "It seems as though people would rather discuss elsewhere. We'll see a blog about one of our articles, and they don't comment on the article [itself]. Somehow a journal doesn't seem like the place to make these short, informal comments," she says.

Certainly, for a public increasingly conditioned to 24-hour media coverage, tweeting, social networks and the open sharing of information, the closed and formal peer-review process is beginning to look increasingly antiquated. The fact that the Séralini paper was published in a peer-reviewed journal also undermines the argument that traditional expert review provides increased confidence in the legitimacy of scientific results.

Earlier this year, a group of Russian researchers from the National Association for Genetic Safety came up with a radical alternative: carry out a year-long rat feeding study as an open, public experiment. The researchers, led by Elena Sharoykina, founder of Moscow's National Association for Genetic Safety, announced they would support the study by crowdfunding. Their intention is to use web cameras, installed in cages with rats, to broadcast all the stages of the feeding experiment online, 24/7. They suggest that by witnessing the experiment, the public will be able to draw its own conclusions and have greater trust in the results. As *Nature Biotechnology* went to press, the site (publicized to go live at the end of March) was not yet live. The question is whether such 'reality' experiments are mere publicity stunts or whether they have more serious implications; do they erode public understanding of the need for the checks and balances of peer review when disseminating scientific results?

Table 1 Feeding studies for assessing chronic effects of transgenic food by length of feeding time or nature of analysis

Reference	Funding agency (where given) or affiliation	Plant species	Animal	Assay	Notes
[23]Brake, D.G. *et al. Food Chem. Toxicol.* **42**, 29–36 (2004)	State of South Dakota Agricultural Experiment Station	Glyphosate-tolerant soybean	Mice	Development of testicular germ cells, which are particularly sensitive to toxic agents	No difference in testicular cell populations, litter size, body weights
[24]Brake, D.G. *et al. J. Agric. Food Chem.* **52**, 2097– 2102 (2004)	State of South Dakota Agricultural Experiment Station	Bt corn	Mice	Development of testicular germ cells, which are particularly sensitive to toxic agents	No difference in testicular cell populations, litter size, body weights
[25]Brasil F.B. *et al. Anat. Rec.* **292**, 587–594 (2009)	Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil	Glyphosate-resistant soybean	Rats	Reproductive tissue histology	Transgenic and organic soy diets caused lower body weights, serum triglycerides, cholesterol, alterations in uterine and ovary morphology
[26]Buzoianu S.G. *et al. J. Anim. Sci.* **91**, 318–330 (2013)	European Union's Seventh Framework Programme (FP7/2007–2013) and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Growth performance, hematological analysis, organ weight and histological analysis	Some differences in offspring of Bt-fed sows (lighter spleen, liver, but overall heavier)
[27]Buzoianu S.G. *et al,PLoS ONE* **7**, e47851 (2012)	European Union's Seventh Framework Programme (FP7/2007–2013) and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Immune function, hematological analysis	Differences in blood chemistry (higher monocyte, lower granulocyte) unrelated to immune function
[28]Walsh M.C. *et al. PLoS ONE* **7**, e36141 (2012)	European Union's Seventh Framework Programme and under grant and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Immune function, hematological analysis, Cry1Ab antibody production and toxin	Perturbations in immune system (lymphocytes higher, erythrocytes lower) in GM diet-fed sows. No translocation of toxin out of GI tract.
[29]Walsh M.C. *et al. Br. J. Nutr.* **109**, 873–881 (2013)	European Union's Seventh Framework Programme and under grant and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Weight, serum chemistry	GM-fed sows heavier, offspring lighter, some difference in serum chemistry
[30]Buzoianu, S.G. *et al. Animal* **6**, 1609–1619 (2012)	European Union's Seventh Framework Programme and under grant and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Body composition, organ weight and histology, urine biochemistry	No effect on growth, organ weight, histology, some differences in serum chemistry
[31]Buzoianu, S.G. *et al. PLoS One* **7**, e33668 (2012)	European Union's Seventh Framework Programme and under grant and the Teagasc Walsh Fellowship Programme	Bt Mon810 (Cry1Ab) corn	Pigs	Relative abundance microbiota in ilium, cecum and feces	No differences except for one genus of unknown importance to health
[32]Daleprane, J.B. *et al. Plant. Food Hum. Nutr.* **64**, 1–5 (2009)	State of Rio de Janeiro Research Assistance Foundation, National Council for Scientific and Technological Development	Glyphosate-resistant soybean	Rats (aged)	Growth rate, protein intake, albumin levels, total serum protein	Organic and GM-fed were heavier, had lower protein intake, reduced hematocrit, than casein fed
[33]Daleprane, J.B. *et al. Braz. Arch. Biol. Technol.* **52**, 841–847 (2009)	State of Rio de Janeiro Research Assistance Foundation and the National Council for Scientific and Technological Development	Glyphosate-resistant soybean	Rats	Protein efficient ration, net protein ratio and coefficient of alimentary effectiveness	Differences were found in body weight ratio, protein intake and quality between the two soybean groups
[34]Daleprane, J.B. *et al. J. Food Sci.* **75**, 126–131 (2010)	State of Rio de Janeiro Research Assistance Foundation, National Council for Scientific and Technological Development (CNPq)	Glyphosate-resistant soybean?	Rats	Growth and weight of aorta, serum lipids	No differences between GM and non-GM
[35]Haryu, Y. *et al. Open Plant Sci. J.* **3**, 49–53 (2009)	National Institute of Animal Health, Kannondai, Tsukuba, Ibaraki, Japan	Cry1a, PAT (Bt11) corn	Mice	Growth, mating, gestation, milking periods, reproduction, life span	No significant difference in performance over five generations, but gradual weight decrease with each generation
[36]Kilic, A., Akay, M.T. *Food Chem. Toxicol.* **46**, 1164–1170 (2008)	Department of Food Safety, Ankara, Turkey	Bt corn	Rats	Histology of stomach, duodenum, liver, kidney, various metabolites and proteins	Minor histological differences in kidney and liver
[37]Krzyzowska, M. *et al. Pol. J. Vet. Sci.* **13**, 423–430 (2010)	Division of Immunology, Warsaw, Poland	Glufosinate-tolerant wheat	Mice	Size of lymph nodes, spleen, blood cells, immunophenotypes of cells from blood and lymph node	GM-triticale leads to expansion of the B-cell compartment in the secondary lymphoid organs, nonallergic and noncarcinogenic
[38]Battistelli S. *et al. Eur. J. Histochem.* **54**, 154–157 (2010)	Agenzia Servizi Settore Agroalimentare delle Marche, Marche, Italy	Glyphosate-resistant soybean	Mice	Histological and ultrastructural characteristics of the epithelium, the histochemical pattern of oblet cell mucins and the growth profile of the coliform population	Similar aging, no effect of transgenic on intestinal structure, but lowered mucin related to diet
[39]Malatesta, M. *et al. Eur. J. Histochem* **47**, 385–388 (2003)	Dipartimento di Scienze Morfologico-Biomediche, Sezione di Anatomia e Istologia, University of Verona, Verona, Italy	Glyphosate-resistant soybean	Mice	Morphometric and immunocytochemical analysis of pancreatic acinar nuclei	Effects on post-transcriptional process of hnRNA in pancreatic acinar cells

(Continued)

Table 1 Feeding studies for assessing chronic effects of transgenic food by length of feeding time or nature of analysis (continued)

Reference	Funding agency (where given) or affiliation	Plant species	Animal	Assay	Notes
[40]Malatesta, M. *et al. Histochem. Cell. Biol.* **130**, 967–977 (2008)	Dipartimento di Scienze Morfologico-Biomediche, Sezione di Anatomia e Istologia, University of Verona, Verona, Italy	Glyphosate-resistant soybean	Mice	Morpho-functional characteristics of the liver	Proteins belonging to hepatocyte metabolism, stress response, calcium signaling and mitochondria were differentially expressed in GM-fed mice hepatocytes; mitochondrial and nuclear modifications indicative of reduced metabolic rate
[41]Malatesta, M. *et al. Cell Struc. Func.* **27**, 173–180 (2002)	Dipartimento di Scienze Morfologico-Biomediche, Sezione di Anatomia e Istologia, University of Verona, Verona, Italy	Glyphosate-resistant soybean	Mice	Ultrastructural morphometrical and immunocytochemical study on hepatocytes	Irregularly shaped hepatocyte nuclei, irregular nucleoli, more abundant nuclear factors
[42]Malatesta, M. *et al. J. Anat.* **201**, 409–415 (2002)	University of Perugia, University of Urbino	Glyphosate-resistant soybean	Mice	Ultrastructure, morphometric, immunocytochemical analysis of pancreatic acinar cells	Influence on zymogen synthesis and processing
[43]Malatesta M. *et al. Eur. J. Histochem.* **49**, 237–242 (2005)	Istituto di Istologia e Analisi di Laboratorio, University of Urbino Carlo Bo, via Zeppi Urbino, Urbino, Italy	GE soybean	Mice	Immunoelectron microscopy of liver	Reversal of changes in hepatocytes
[44]Vecchio, L. *et al. Eur. J. Histochem.* **48**, 448–454 (2004)	Italian Ministry of University and Research and by the Fondo di Ateneo per la Ricerca, Pavia University, Pavia, Italy	Glyphosate-resistant soybean (NK103)	Mice	Immunoelectron microscopy of Sertoli cells, spermatogonia and spermatocytes	Immunolabeling of cells in testes showed differences
[45]Séralini, G.E. *et al. Food Chem. Toxicol.* **50**, 4221–4231 (2012)	Association CERES, the Foundation "Charles Leopold Mayer pour le Progrès de l'Homme", the French Ministry of Research, and CRIIGEN, Caen, France	Glyphosate-resistant maize	Rats	Life span, liver and kidney morphology	Death and tumor rates higher in some treated groups
[46]Rhee, G.S. *et al. J. Toxicol. Environ. Health A* **68**, 2263–2276 (2005)	Korean FDA	Bialophos-resistant potato	Rats	Body weight, food consumption, reproductive performance and organ weight	No changes in body weight, food consumption, reproductive performance, and organ weight
[47]Sakamoto, Y. *et al. J. Food Hyg. Soc. Japan* **48**, 41–50 (2007)	Japanese Health Ministry	Glyphosate-resistant soybean	Rats	Hematology, serum biochemistry and pathological examinations	Body weight, food intake unchanged, hematological, serum biochemistry, organ weights unchanged. No increased incidence of neoplasms
[48]Sissener, N.H. *et al. Aquaculture* **294**, 108–117 (2009)	Norwegian Research Council	Glyphosate-resistant soybean	Salmon	Growth, body composition, organ development, hematological parameters, clinical plasma chemistry and lysozyme levels	Plasma triglycerol levels elevated, mid-intestine smaller; no differences in total growth or other parameters measured
[49]Steinke, K. *et al. J. Anim. Physiol. Anim. Nutr.* **94**, 185–193 (2010)	University of Munich	Cry1ab Bt (Mon 810) corn	Cow	Dry matter intake, lactation, milk yield	No effect on milk composition or body condition
[50]Trabalza-Marinucci , M. *et al. Livest. Sci.* **113**, 178–190 (2008)	Italian Ministry of Health	Cry1Ab (Bt 176) corn	Sheep	Performance, reproductive traits, hematological parameters, antioxidant defenses, lymphocyte proliferative capacity, phagocytosis and intracellular killing of macrophages, and ruminal microbial population characteristics	No difference in performance, reproductive traits, blood parameters, immune system, microscopic changes in liver nuclei
[51]Tudisco, R. *et al. Animal* **4**, 1662–1671 (2010)	Università di Napoli, Università di Catanzaro Magna Græcia, Università di Napoli	Glyphosate-resistant soybean	Goats	Enzyme activities in serum, heart, kidney, skeletal muscle, liver	Increase in lactate dehydrogenase activity in heart, muscle, kidney; body and organ weight unchanged
[52]Velimirov, A. *et al.* Research Reports, Institute of Nutrition and Research Institute of Organic Agriculture, Vienna, Austria (2008)	Austrian government	Stacked corn (MON 810, NK603) Bt and glyphosate-resistance	Mice	Cell and organ microscopy and histology, gene expression pattern, litter size and weight	Effect on reproduction

Bt, *Bacillus thuringiensis*.

performed, the length of time covered and the test animal used (**Table 1**). Moreover, in only a few cases have there been follow-up studies either by the original authors or others, all of which makes it challenging or impossible to draw firm conclusions from the existing body of literature. Publications from the industry itself account for only 20% of the peer-reviewed literature. Finally, the number

of traits for which any feeding studies, long or short term, exist in the literature is small compared with the number of traits that have completed their consultation at the FDA (**Table 2**). However, it is difficult to draw a line from that group of traits or the genetic events that contain them to what is being grown and sold for food in the marketplace.

Only a few groups have conducted in-depth analyses (**Table 1**), including a team associated with the Teagasc Food Research Centre in Ireland (funded under the EU 7th Framework), which found that a diet of *Bt* maize caused no long-term deleterious effects on the digestive and immune systems of pigs; a group of Italian researchers (supported by the Italian Ministry of Health), who over the years have identified some deleterious effects of glyphosate-resistant soybean on the morphology and histology of detoxifying organs in rodents and a group in South Dakota (supported by the state's agriculture extension program), who in the early 2000s, found no significant long-term effects of transgenic crops on testicular development in mice.

Chassy questions whether long-term feeding studies are even necessary. "These kinds of feeding studies are extremely weak, they have no power to distinguish between groups, are fraught with differences that are not biologically significant between groups from simple variation and probability. They are hypothesis-less fishing trips." On the other hand, the Union of Concerned Scientists' Doug Gurian-Sherman says a test that is 90 days or shorter is a poor surrogate. "I don't see how you can make strong conclusions about long-term effects based on relatively short-term tests with relatively small numbers of animals. They are both weaknesses."

VU University's Katan also sees problems with the current system. "Ninety-day rat trials are more or less dogma for the lack of anything else. Of course, you have to do something. You can't just sit there and tell the industry, well we're not certain so just go ahead and do your thing and spread it around and if it causes cancer, we'll find out." But he believes better animal models and conducting a power analysis—a statistical procedure that determines the number of required subjects needed to show a difference at a predetermined level of significance and size of effect—before launching a feeding study, would improve outcomes. "You have to be very much aware of what is being tested for, what are the variabilities in the outcome, how much of an effect do I want to pick up and how many animals do I need to pick that up with reasonable confidence. I see very little of that in animal experiments," he says.

Lynn Goldman, epidemiologist and dean at the School of Public Health at The George Washington University in Washington, DC, and a member of the National Academy of Sciences panel convened in 2004 to assess the risk of GM foods[15], says that 90-day feeding studies remain a useful tool, but they have their drawbacks. "What they'll tell you is whether there's a toxin so I wouldn't say don't do them. What they don't tell you is whether there's a toxin that works very slowly. If it's a toxin that kills you that's one thing, but what if it causes neurological damage, something that is more like Parkinson's?"

Table 2 Transgenes under review and study

	Approved for commercial sale (ISAA GM approval database)	Published safety data exists
Trait	**Gene**	**Gene**
Herbicide tolerant	*Aad-1,2 (2,4-D), dmo* (dicamba), *bar, pat, syn pat* (glufosinate), *2meEPSPS, cp4 EPSPS, Ag EPSPS, gat4601, gat4621, goxv247* (glyphosate), *hppdPF W336*(isoxaflutole), *bxn* (oxynil), *als, csr1-2, gm-hra, S4-hra, surB, zm-hra* (sulfonylurea)	*Pat, CP4 EPSPS, gat,* mutated *als*
Anti-allergy	*7crp*	
Antibiotic resistance	Aminoglycoside, ampicillin, neomycin, streptomycin	
Coleopteran insect resistance	*Cry34Ab1, cry35Ab1, cry3A, cry3Bb1, mcry3A*	*Cry34Ab1, cry35Ab1*
Delayed fruit ripening	*Aac* (truncated) *accd, anti-efe, sam-k*	
Drought stress tolerance	*cspB, EcBetA, RmBetA*	
Fertility restoration	*Barstar, ms45*	
Lepidopteran insect resistance	*Cry1A, cry1A.105, cry1Ab,trun. Cry1Ab, cry1Ab-ac, cry1Ac, cry1C, cry1F, cry1Fa2, cry2Ab2, cry2Ae, cry9c, mocry1F, pinII, vip3A, vip3Aa20*	*Cry1Ab, cry1F, cry9c, vip3A*
Male sterility	*Barnase, dam, zm-aa1*	
Mannose metabolism	*pmi*	
Modified alpha-amylase	*Amy797E*	
Modified amino acid	*corpdapA*	*corpdapA*
Modified oil, fatty acid	*Fad2-1A, fatb-1A, gm fad2-1* (silencing), *NcFad3, pj.D6D, te*	*FAD-1* fragment
Modified starch/carbohydrate	*Gbss* (antisense)	
Multiple insect resistance	*AP1, CpT1, ecry31Ab*	
Nopaline synthesis	*nos*	
Phytase production	*phyA, phyA2*	
Viral resistance	*Ac1* (sense, antisense), *cmv-cp, plrv-orf1, plrv-orf2, ppv-cp, prsv-cp,prsv-rep, pvy-cp, wmv-cp, zymv-cp*	Potato virus polymerase, potato virus non-translated regions
Visual marker	*dsRed2, uidA*	

Reality checks

Critics and proponents of genetically modified organisms (GMOs) alike agree that genetically modified foods have failed to produce any untoward health effects, and that the risk to human health from foods contaminated with pathogens is far greater than from GMOs. The US Centers for Disease Control (CDC; Atlanta) reports that in 2012, there were 128,000 cases of food-borne illnesses leading to hospitalizations, with 3,000 deaths (http://www.cdc.gov/foodborneburden/index.html). Contrast that with none reported for transgenic foods in their decade-long history in the food supply. However, there has been no concerted effort to find out whether transgenic food has long-term effects on animal health, partly because of a lack of funding and partly because there is no consensus on how to carry out such studies. Of the over 100 peer-reviewed feeding studies done to assess such risks (**Supplementary Table 1**), the majority are short-term studies on a small number of traits, which would not reveal any chronic effects from long-term consumption of transgenic foods. And, absent food labeling or otherwise tracking transgenic foods, the impact of transgenic foods on those consuming it cannot be known.

This may explain in part why, after transgenic products have been in the human food chain for more than a decade without overt ill effects, doubts persist.

Whereas some argue that genetic engineering is different from conventional breeding technologies and thus requires special oversight, others argue the opposite, pointing out that humans have been genetically modifying plants and animals for millennia. To be sure, there is no evidence that transgenesis itself alters crop characteristics in a way that presents a threat to human health. One could equally argue that the system of food safety oversight should be the same for all new breeds of crops, regardless of the method of production—the approach taken by US regulators since transgenic crops first entered the US food supply. Yet, public uneasiness about transgenic products, fueled by sensational food stories in the media, misinformation from ideological opponents of transgenic crops and maneuvering on the part of politicians, continues to maintain pressure on regulators to scrutinize transgenic food products more carefully than traditionally bred products and even those generated by alternative breeding methods, such as chemical or irradiation mutagenesis.

Against this background, the system of food safety oversight is an imperfect one, our understanding of all the factors that affect food safety remains incomplete and the bounds of scientific knowledge and technology continue to expand. This often conflicts with the expectations of a public that seeks definitive and absolute answers to questions of food safety—a public that does not understand why, a decade or more after transgenic products entered the food supply, papers are still being published that question their safety.

Most of the transgenic food that we currently eat (Roundup Ready soy, for example) is embedded in a variety of processed foods (at very low concentrations). And measuring the effects of a complex foodstuff, in which a transgenic ingredient may be one of many components, in the milieu of a typical diet, is extremely challenging. Such effects are likely to be vanishingly small and obscured by numerous confounding variables.

And Chassy suggests that these are paradoxical concerns. "A key problem with the toxic new metabolite scenario is that while there are hundreds of potentially toxic molecules found in crop plants, virtually none of them is ever present at a concentration that would do harm—which is a good thing for those of us that like salads! If a new metabolite were to appear, odds are that it would not be present at a concentration sufficient to cause harm," he reasons. "If it were," Chassy points out, "it would be easily detectable."

Much of the thinking currently views 90-day feeding studies as a reasonable surrogate for assessing the long-term effects of ingestion of new food (transgenic or otherwise). Indeed, our survey of the published literature reveals that very few feeding studies longer than 90 days have ever been carried out. Thus, there is scant evidence, one way or the other, about the long-term effects of transgenic foods, or any other foods, on animal health.

Not only are these long-term feeding studies difficult to execute, but also those who are best placed to fund them (i.e., seed companies) have no motivation to spend the time, money and effort involved in doing them. Given the lack of evidence for harm, the onus is on others (who regard this as a key lacuna in our knowledge of food safety) to find funding for such studies. But where should this funding come from? Opponents of transgenic technology often summarily dismiss as biased and untrustworthy food safety studies carried out by industry. If such a viewpoint is valid, then studies funded by the organic lobby or opponents of transgenic technology showing a negative effect may also be perceived to be biased and untrustworthy. If independent government bodies will not step up, crowdsourcing has been suggested as a way of raising funds for long-term feeding studies (**Box 1**).

Clearly, the amount of testing carried out on a new food should be in proportion to the nature and magnitude of the risk associated with it. According to Marion Nestle, professor of nutrition, food studies and public health at NYU, there are two ways of looking at the problem of real risk versus perceived risk. From the standpoint of the risk of illness, hospitalization and death, the reality is that transgenic food is a very low risk (by far the most serious problem is food poisoning through microbial contamination).

But perception about food safety depends on how risk is communicated and whether the food is familiar or foreign, natural or technical. "You have this dichotomy where the biggest problem of food safety is bacterial or viral illness. But because [cases of food poisoning] are familiar not technical, understood, not imposed, somewhat voluntary, people don't get upset about them." In contrast, she says, "people get very upset about food biotechnology because it's foreign, unfamiliar, technological and imposed, even though there is very little evidence for harm."

Beyond these issues, decreasing trust in institutions as a whole is likely to erode the public's confidence in a food safety regulatory process that is less than transparent. In a similar way to increasing calls for the release of data used to support applications of drug products and greater post-marketing oversight of drugs, it is possible that calls for post-marketing studies of transgenic foods may also become an issue as society becomes more open. It does not help that Monsanto leads the agribusiness sector in lobbying spending, according to OpenSecrets.com.

Putting aside the question of who would pay for these studies, George Washington University's Goldman offers several possible scenarios, from labeling food to putting a barcode into the food itself that identifies what exact variant is in the food. Alternatively, products could be followed through the supply chain, she suggests. "People can tell you where they get their food, and what brands they eat. There are a lot of different ways [of tracking food]," she says. NYU's Nestle remains skeptical about post-marketing studies, however. They "are very, very difficult to do," she says. "Unless there's something really wrong, you're not going to be able to attribute it to a particular food." Certainly, whether one runs an epidemiological study or randomized, controlled clinical trial, it will be a daunting challenge to find suitable population cohorts in which people have consumed a food containing a transgenic component(s) and another equally matched control group has not.

Thus, the circularity of the debate on the safety of transgenic food, the length of time over which the same issues have been contested, addressed and revisited, and the limited ability of the scientific community to counter misinformation surrounding transgenic food suggest that these products will continue to court controversy. As Gurian-Sherman puts it, the problem is a societal one. "Clearly how much risk and how much uncertainty is accepted is a social decision, a public decision. It is not a scientific decision."

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.2686).

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Corrected after print 26 September 2013.

Erratum: How safe does transgenic food need to be?

Laura DeFrancesco

***Nat. Biotechnol.* 31, 794–802 (2013); published online 10 September 2013; corrected after print 26 September 2013**

In the version of this article initially published, on page 795, reference was made to a paper that argues that 90-day feeding studies should only be done when deemed necessary, with the implication that EFSA had authored the paper. While EFSA does take that position, the paper was authored by scientists at the RIKILT Wageningen UR (H.A. Kuiper and E.J. Kok) and The James Hutton Institute (H.V. Davies). In addition, the EU project described by Esther Kok on page 796 was incorrectly identified as the GMSAFOOD Initiative. It should have read SafeFoods. The errors have been corrected in the PDF and HTML versions of this article.