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Science, Law, and Politics in the Food and Drug Administration's Genetically Engineered Foods Policy: FDA's 1992 Policy Statement

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The US Food and Drug Administration's (FDA's) 1992 policy statement was developed in the context of critical gaps in scientific knowledge concerning the compositional effects of genetic transformation and severe limitations in methods for safety testing. FDA acknowledged that pleiotropy and insertional mutagenesis may cause unintended changes, but it was unknown whether this happens to a greater extent in genetic engineering compared with traditional breeding. Moreover, the agency was not able to identify methods by which producers could screen for unintended allergens and toxicants. Despite these uncertainties, FDA granted genetically engineered foods the presumption of GRAS (Generally Recognized As Safe) and recommended that producers use voluntary consultations before marketing them.

Key words: unintended effects, food safety, scientific uncertainty

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INTRODUCTION

Agricultural biotechnology has the potential to help address a wide range of public health, nutritional, agricultural, and environmental problems in developed and developing countries, as described in a variety of scientific,[1] government,[2] industry,[3] and international[4,5] sources. Despite this potential, the commercialization of the first generation of crops based on these technologies has met with concern and protests from consumer and public interest groups,[6-8] environmental groups,[9] and some governments and scientists (for example, the Union of Concerned Scientists: http://ucsusa.org/food_and_environment/index.cfm). This conflict has grown to such proportions that it has banned or slowed commercialization or use of these products in some countries,[10] disrupted the distribution of food aid in drought-stricken southern Africa,[11] reduced US exports of major commodities,[12] affected the value of Wall Street stocks for major agricultural biotechnology companies,[13] and become a major issue of contention in the regulation of international trade.[13]

Many of the proponents of agricultural biotechnology have suggested that the issue should be resolved through the application of sound science,[14] and that it would be unethical to ban or inhibit the potential benefits associated with this technology for addressing serious problems related to public health, nutrition, poverty, and the environment.[15,16] Many of the critics have called into question the adequacy of the scientific knowledge,[17,18] questioned the benefits, raised concerns regarding the potential risks,[19] and claimed that regulatory decisions have been based more on politics than on science.[20,21]

Nutrition scientists and professionals are implicated in this debate in many ways. First, many are (or could be) conducting research, accepting funding, and/or playing professional roles that affect or are affected by the ways in which this technology is incorporated into the food system. Second, many members of the public, including students, consumers, journalists, and legislators, may look to us to interpret and offer guidance regarding this technology and its controversies. However, developing an informed view is problematic in this case because of the sharply divergent interpretations presented in the literature.

This paper is especially timely for the nutrition community. In contrast to the first generation of genetically engineered (GE) crops that have been designed to address production problems, the second-generation crops currently under development are expected to include a much wider range of alterations, including nutritional alterations. These may include changes in the levels and types of specific fatty acids, vitamins, minerals, phytochemicals, anti-nutrients such as phytase, and, potentially, some substances presently found in dietary supplements. Many in industry view this as

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the beginning of a new era of marketing opportunities based on the ability to make health claims for "functional foods." However, many in the nutrition science, public health, and consumer interest communities are concerned that these products and health claims will create further confusion among consumers and far exceed the scientific evidence concerning effectiveness and potential unintended health and nutritional consequences. To a significant degree, the direction, pace, and effects of these developments will depend upon the regulations that the US Food and Drug Administration (FDA) puts in place related to health claims, premarket testing, standards for food safety, and labeling.

This paper is part of a larger research effort to examine how science, law, and politics interacted in the development of regulations for the first generation of GE crops so that nutrition scientists, regulators, and others can consider what changes, if any, should be made in the future. The present paper describes sources and methods, provides a timeline of key regulatory events, and examines in detail the regulatory frameworks and scientific issues identified in FDA's 1992 statement of policy.[22,23] This detailed examination of the 1992 policy is provided on the assumption that many nutrition scientists and professionals are not familiar with the actual details of FDA's official policy and its controversial scientific and legal justifications. A second paper examines scientific concerns and knowledge gaps in greater detail.[22] A third paper examines legal and political considerations (Pelletier D, unpublished data, 2005).

SOURCES AND METHODS

An important feature of the methods used in this research is the heavy reliance on primary sources, such as Federal Register documents, reports from the National Research Council, and internal FDA memos, with the use of direct quotes in many cases. These methods are used because most of the debate concerning the regulation of GE foods is based on second- and third-hand representations and interpretations of FDA's policy. Such a debate is highly prone to perpetuate the intentional or unintentional distortions and biases of various parties, especially in light of the scientific and legal complexities and ambiguities posed by GE foods. The use of direct quotes serves to establish FDA's official interpretations and conclusions regarding scientific and legal matters. The use of primary sources more broadly serves to re-ground the debates in the "primary data," in keeping with the established norms for deliberation in science and law. Readers are encouraged to consult these primary sources directly to help form their own judgments on the issues raised in these papers.

More specifically, this research relies most heavily upon the following methods and original sources:

1. Detailed presentation of issues identified in FDA's 1992 statement of policy, including verbatim quotes, to reveal how the 1992 policy addresses key issues and the stated scientific, legal, and other justifications for FDA's decisions.
2. Concerns raised by FDA scientists and senior scientific administrators in internal correspondence. These sources are particularly relevant in this context because the courts routinely grant deference to agency decisions when technical matters are involved, thus the views of the scientific staff are critically important.
3. Statements, conclusions, and recommendations from expert committees of the National Academy of Sciences and the National Research Council as a "quasi-independent" source of judgments concerning scientific issues and the adequacy of regulatory procedures in FDA's 1992 policy.
4. Analysis of the regulatory history related to GE foods, assembled from diverse documents in the Federal Register, to clarify which institutions were responsible for various decisions and the justifications for those decisions.
5. Analysis of legal arguments and decisions arising from a lawsuit brought against FDA.
6. Analysis of additional FDA documents such as its proposed rules for GRAS (Generally Recognized As Safe) determinations (1997) and proposed revisions to its GE foods policy (2001).

Finally, the account emerging from the above sources was verified and amplified by interviewing knowledgeable individuals, including current and former government officials, members of non-governmental organizations, and academics.

TIMELINE

Table 1 presents a timeline of key events related to the development of agricultural biotechnology policy in general, and FDA's policy in particular. Policy developments are shown on the left, and a variety of scientific and societal events that shaped and/or responded to policy development are shown on the right. The policy developments shown here are described in detail in these papers. Due to space constraints, the societal developments are not addressed in detail, but are well-described in a number of other sources.[24-26]

REGULATORY FRAMEWORK

In 1992, FDA published *Statement of Policy: Foods Derived from New Plant Varieties*,[23] in response to numerous requests from industry, academia, and the public to clarify its interpretation of the existing regulatory frameworks as they pertain to plant varieties produced by "the newer methods of genetic modification." The 1992 policy state-

ment included a review of scientific issues relevant to food safety, the regulatory status of GM foods, labeling, and guidance for industry describing how they might meet FDA's regulatory requirements before marketing GM foods. The guidance for industry consists of five decision trees and accompanying text detailing the types of considerations and safety tests that might be performed under various circumstances. As a legal matter, FDA's 1992 policy statement represents an interpretation of how existing regulations are to be applied to GM foods, reflecting FDA's view that the "newer techniques of plant breeding" (rDNA) do not pose any fundamentally new risks requiring new regulations. This legal status of the 1992 policy has important implications, as described in paper three of this series (Pelletier D, unpublished data, 2005).

FDA asserted in 1986 that it had sufficient authority to regulate GM foods under either the adulteration clause, section 402(a)(1) of the Federal Food, Drug and Cosmetic Act, which normally governs whole foods, or under the food additives clause, section 409, which normally governs chemical substances added to foods to achieve an intended effect.[27] However, GM foods pose a challenge to this binary choice because they are whole foods and have also been altered to achieve an intended effect through the "addition" of new segments of DNA and, indirectly, the intended expression product(s). In resolving this issue, FDA had to proceed carefully because the choice would have profound implications for the level and type of premarket testing required, the strictness of the legal safety standard, labeling, the burden of proof placed on developers versus FDA, the administrative burden on FDA for product reviews, and, ultimately, the pace with which GM foods would enter the marketplace. As noted in the timeline, these policies were being developed throughout the 1980s and early 1990s, when de-regulation and international competitiveness were dominant themes in federal politics and policymaking.

The food additive clause (section 409) mandates that producers file a "food additive petition" with FDA before marketing foods containing an additive, and usually requires that producers perform extensive safety testing to demonstrate that there is "reasonable certainty of no harm" when the additive is used as intended. If successful, this petition results in an affirmative statement from FDA, in a letter to the producer, stating that the food additive has been approved. All approved food additives must be listed on the ingredient section of the food label. Some added substances can be exempted from the food additive petition process under the GRAS clause if they have a long history of safe use (e.g., spices, vinegar, natural flavors) or have been determined to be GRAS on the basis of publicly available evidence and in the judgment of qualified experts.

The adulteration clause is the authority under which FDA normally regulates (and recalls) whole foods to guard against microbiological, chemical, or physical contamination. The 1992 policy states:

> Section 402(a)(1) of the act will be applied to any substance that occurs unexpectedly in the food at a level that may be injurious to health. . . . It is the responsibility of the producer of a new food to evaluate the safety of the food and assure that the safety requirement of section 401(a)(1) is met.[23]

Under this clause, FDA typically defines enforcement guidelines known as "action levels" for various contaminants when the identity of those contaminants is known. The prospect of adverse publicity and the threat of legal action normally creates an incentive for industry to adhere to these guidelines and associated good manufacturing practices. However, unlike the food additive clause, there is no mandate for premarket testing nor ex ante demonstration that the food is not adulterated. Instead, because these substances occur unexpectedly, by definition, a problem with the food typically might be revealed through post-marketing testing, surveillance, adverse event reports, and/or outbreaks of illness. In the case of new substances or substances for which action levels have not been defined previously, the food would be considered adulterated "if, by virtue of the added substance, there is a 'reasonable possibility' that consumption of the food will be injurious to health."[23]

Thus, the food additive clause generally provides greater ex ante assurance of safety for new substances, but is more burdensome for producers and for FDA, while the adulteration clause generally relies upon good manufacturing practices and post-marketing detection and recall authority to protect public health.

In its 1992 policy, FDA avoided exclusive use of either the food additive clause or the adulteration clause and instead opted for an amplified version of the adulteration clause as a type of middle ground. Specifically:

- There was no mandate for premarket testing or approval;
- GE foods, as with other whole foods, were presumed to be GRAS by FDA unless the details in a specific case suggested otherwise;
- Developers of GE foods, as with developers of other whole foods, were allowed to independently judge whether the new variety was GRAS;
- Developers could voluntarily follow a set of decision trees provided by FDA to guide their GRAS determination and testing on a case-by-case basis;
- Developers were urged to voluntarily consult with FDA at the beginning of this process when deciding the protocols they would follow and again at the end to review their findings; and
- If successful, this process does not result in an affirmative approval letter from FDA, as with food additives, but a letter that simply reiterates the con-

Table 1. Timeline of Key Events in the Development of the Genetically Engineered Foods Policy

Year	Policy Developments	Societal and Scientific Events
1973	Gordon Conference on safety of bacterial rDNA experiments	Boyer and Cohen gene transfer Singer and Soll letter in *Science*
1975	Asilomar Conference Voluntary moratorium enacted	
1976	NIH RAC formed; safety procedures developed	Citizens in MA and CA protest rDNA research
1978	Extensive research and containment procedures address safety questions	rDNA bacterium produces insulin
1979		Public protests of rDNA research subside rDNA bacterium produces human growth hormone
1980	Diamond v Chakrabarty, permits gene patents	Cloned bacteria produce interferon
1981		President Reagan initiates de-regulation
1983	Gore hearings reveal lack of scientific evidence on environmental safety	Ice-minus bacterium developed First rDNA transformation of a plant, with kanamycin resistance gene
1984	Bayh-Dole Act allows university patents Biotech working group formed	Regulatory uncertainty hinders biotech research NRC, promotional report
1985	BSCC formed	NRC, promotional report
1986	OSTP Coordinated Framework FDA, USDA, EPA clarify policies Monsanto executives visit VP Bush	
1987	Public comments question the scope of oversight proposed by agencies BSCC attempts to resolve oversight conflicts	NRC, promotional report •Ice-minus open-air testing •NAS white paper defines key principles
1988	Regulatory uncertainties continue	NAS/FNB annual symposium report
1989	BSCC unable to reach consensus OSTP forwards issues to Quayle Council	NRC, rDNA Introductions into the environment L-tryptophan food supplement kills two dozen people
1990	OSTP proposes Scope of Oversight	
1991	Quayle Council shapes oversight policy FDA begins review of FlavrSavr tomato	Gulf War
1992	OSTP finalizes Scope of Oversight FDA issues Statement of Policy USDA issues proposed rules	Biotech industry rejoices in FDA policy, though some object to political influence in its development 4000 citizens request labeling
1993	USDA finalizes its rules	rBST approved by FDA; public protests ensue Monsanto adopts aggressive strategies under new CEO (Shapiro)
1994	FDA approves FlavrSavr tomato	rBST protests subside
1995	EPA approves Bt corn	UK/EU approve Roundup Ready soybeans
1996		GM maize and soybean commercialized in US UK acknowledges BSE in human deaths

(Table continues on next page.)

Table 1. Timeline of Key Events in the Development of the Genetically Engineered Foods Policy (Cont'd)

Year	Policy Developments	Societal and Scientific Events
1997	FDA clarifies its consultation policy EPA finalizes its regulations USDA eases its regulations	Public protests begin in Europe
1998	EPA approves Starlink corn for animal feed	Pustzai's disputed GM potato studies Bio-Integrity sues FDA
1999	GE foods become US/EU trade issue FDA holds three public meetings in response to conflict and receives 35,000 public comments thereafter	European retailers reject GM food UK imposes three-year ban on new GE crops EU mandates labeling for GE foods UN Biosafety protocol blocked by US+4 Lossey's disputed monarch butterfly study Seattle protests of WTO, TNCs, GE foods, etc Golden Rice announced and denounced
2000	NRC, Health and Environmental Safety of Pest-protected Plants Bio-Integrity's suit of FDA dismissed	UN biosafety protocol adopted Starlink corn detected in human food supply
2001	FDA proposes mandatory pre-market notification for new GE foods	Starlink removed from human food supply
2002	NRC, Environmental Effects	Chapela and Quist's disputed Mexican maize study Southern African drought and GM food aid debates NRC report on safety of animal biotechnologies Conflict between bio-pharmers and food farmers Pharm-maize contaminates soybean field
2003		US files WTO lawsuit against EU
2004	NRC/IOM, Safety of Genetically Engineered Foods	

clusions the developer has drawn and states "FDA has no further questions."

In effect, these guidelines allowed most foods to avoid the higher requirements of the food additive petition process but do provide for a greater degree of (voluntary) consultation between FDA and developers than is the case with non-GE whole foods. In practice, FDA believes all new varieties marketed to date have gone through the consultation process, but the details on the testing protocols and consultations are not readily available to the public.

FDA's logic and the decision trees achieve this regulatory middle ground, in effect, by treating the intended expression products of the transgene (as well as metabolically related nutrients, known toxicants, and known allergens) as the primary focus of premarket assessment by developers, and treating any unexpected (e.g., pleiotropic or insertional mutagenic) effects of the transformed variety as being subject to the post-marketing adulteration clause.[28]

This approach responded to two powerful considerations: a) a desire to minimize the regulatory interference with this industry[29]; and b) the gaps in scientific knowledge, evidence, and testing methods, especially concerning the unintended consequences of transgenic breeding of food crops, which made it difficult or impossible to produce affirmative evidence of the presence or absence of unintended harmful changes in the new variety.[22]

The lack of evidence and testing methods related to the unintended effects of genetic engineering is a fundamental consideration when interpreting the conflicting and contradictory claims related to GE foods. It means that statements from government, industry, and other groups to the effect that "there is no evidence that any of the GE foods currently on the market have caused harm or are unsafe to eat" is primarily a statement about the lack of evidence rather than a statement regarding lack of harm. It also means that statements from consumer or public interest groups about the dangers or risks of GE foods are primarily statements about the potential for harm rather than demonstrated harmful effects. The manner in which FDA's 1992 policy statement addressed these issues is analyzed below.

SCIENTIFIC ISSUES

FDA's Statement of Policy

In its 1992 statement of policy, FDA notes that a spectrum of techniques exists for genetic modification, including traditional breeding, mutagenesis, somaclonal

variation, wide-cross hybridization, protoplast fusion, and, more recently, rDNA techniques. FDA notes that all of these techniques have the potential to introduce extraneous genetic material and undesirable traits and, thus, they require extensive backcrossing with the parent line to achieve the desired results. Moreover, it asserts that rDNA techniques are superior in this regard because:

> In theory, essentially any trait whose gene can be identified can be introduced into virtually any plant, and can be introduced without any extraneous material. Since these techniques are more precise [than other forms of genetic modification], they increase the potential for safe, better-characterized and more predictable food.[23]

This logic forms the basis for FDA's position that rDNA techniques are simply an extension of genetic modification that has been used by humans for thousands of years, that it creates no fundamentally new risks, and that it is more precise and predictable than traditional plant breeding.

Although rDNA techniques may be more precise with respect to the genetic material being transferred, this is not the only relevant consideration. Specifically, FDA notes there are scientific reasons why the insertion of the material and the phenotypic effects are not entirely predictable:

> DNA segments introduced using the new techniques insert semi-randomly into the chromosome, frequently in tandem multiple copies, and sometimes in more than one site on the chromosome. Both the number of copies of the gene and its location in the chromosome can affect its level of expression, as well as the expression of other genes in the plant. . . . Additionally, as with other breeding techniques, the phenotypic effects of a trait may not always be completely predictable in the new genetic background of the host.[23]

Since that time, these possibilities have come to be referred to as "insertional mutagenesis."

FDA's policy statement notes that in other forms of plant breeding, a limited number of backcrosses are often performed to enhance the stability of the line and the ability to cross the trait into other lines, but this practice focuses on stabilizing the expression of the desired trait. FDA does not indicate whether it also serves to eliminate the unexpected phenotypic effects referred to above. With respect to unintended effects, FDA states that all breeding or genetic modification techniques have the potential to create these, but states: "plant breeders using well-established practices have successfully identified and eliminated plants that exhibit unexpected, adverse traits prior to commercial use."[23] This statement of reassurance, which appears in several places in the statement of policy, does not describe these practices and their efficacy for detecting and eliminating subtle compositional changes in the final food product, but some indications are provided in one passage, which states:

> The established practices that plant breeders employ in selecting and developing new varieties of plants, such as chemical analyses, taste testing and visual analyses, rely primarily on observations of quality, wholesomeness and agronomic characteristics. Historically these practices have proven reliable for ensuring food safety.[23]

In summary, while stronger methods are available to assess the safety of the intended expression products from the transgene (described below), the statement of policy seems to imply, but does not actually state, that the traditional plant breeding methods described above might be sufficient to also detect or reduce potential unintended toxicologic, allergenic, or compositional effects arising from insertional mutagenesis and pleiotropy. Some excerpts dealing specifically with toxicants and allergens are examined below.

Toxicants

One class of potential unintended effects from genetic modification relates to toxicants. FDA lists several known toxicants found in specific foods (e.g., protease inhibitors in some cereals, lectins and cyanogenic glycosides in some legumes, cucurbiticin in squash and cucumbers, and lathyrogens in chickpeas), and notes that many of these occur at levels that do not cause acute toxicity, while others may cause severe illness or death if foods are not properly prepared.

FDA's policy statement notes the potential for creating new toxicants through plant breeding:

> Plants, like other organisms, have metabolic pathways that no longer function due to mutations that occurred during evolution. Products or intermediates of some such pathways may include toxicants. In rare cases, such silent pathways may be activated by mutations, chromosomal rearrangements or new regulatory regions introduced during breeding, and toxicants hitherto not associated with a plant species may thereby be produced. Similarly, toxicants normally produced at low levels in a plant may be produced at high levels in a new variety as a result of such occurrences.[23]

The statement of policy goes on to say that the likelihood of this occurring is "considered extremely low in food plants with a long history of use that have never exhibited production of unknown or unexpected toxins."[23]

As distinct from silent pathways, unexpected toxicants also can be created through insertional mutagenesis and pleiotropic effects, but the policy statement does not express a view regarding the likelihood of these occur-

ring and whether these are more likely in genetic engineering than in other forms of plant breeding. FDA's proposed rules in 2001 expressed the view that such effects are more likely with genetic engineering than with traditional breeding, this being one of the justifications for proposing mandatory premarket notification at that time.[30] However, this was a reversal from the 1992 policy statement, which simply implied that the methods plant breeders have used in the past will be adequate for genetic engineering as well.

FDA's guidance to industry includes several general suggestions for how developers might approach the assessment of new plant varieties for known or unexpected toxicants. In one passage, it states:

> It is not possible to establish a complete list of all toxicants that should be considered for each plant species. In general, the toxicants that are of highest concern are those that have been documented to cause harm in normal or animal diets, or have been found at unsafe levels in some lines or varieties of that species or related species. In many cases, characteristic properties (such as bitter taste associated with alkaloids) are know to accompany elevated levels of specific natural toxicants. If such characteristics provide an assurance that these toxicants have not been elevated to unsafe levels, analytical or toxicological tests may not be necessary.[23]

In those cases in which more detailed analytical tests do seem warranted, FDA notes that the interpretation of such tests is complicated by the great variation that exists in levels of naturally occurring toxicants within and between varieties, and that great uncertainty exists concerning safe ranges. Thus, it states:

> In some cases, analytical methods alone may not be available, practical, or sufficient for all toxicants for which levels need to be assessed. In such situations, comparative toxicological tests on new and parental varieties may provide assurance that the new variety is safe. FDA encourages producers of new plant varieties to consult informally with the agency on testing protocols for whole foods when appropriate."

This section of the 1992 policy suggests that the new variety should be compared with parental varieties and/or with untransformed varieties as a screen for potentially significant changes. It notes that this is consistent with the concept of substantial equivalence, as developed by the Organization for Economic Co-operation and Development (OECD), and with principles discussed in a joint Food and Agriculture Organization/World Health Organization report.[31] FDA's 1992 policy states that comparisons should be made of the following: a) toxicants and allergens known to occur in the host or donor species; b) concentration and bioavailability of important nutrients for which a crop is ordinarily consumed; c) safety and nutritional value of newly introduced proteins; and d) the identity, composition, and nutritional value of modified carbohydrates, fats, or oils.

The concept of substantial equivalence has been further explicated, defended, and critiqued since that time[32-34] and is one of the subjects discussed by a recent Institute of Medicine committee.[35] It suffers from ambiguity concerning what constitutes a meaningful difference in composition, how much statistical power should be present to detect such differences, and whether the new variety should be compared only with the parental variety grown under identical conditions or with the range of values for all untransformed varieties grown under varying conditions. Moreover, as invoked by FDA in 1992, it would not permit identification of unexpected toxicants, allergens, and/or nutrition-relevant changes because effective techniques for metabolic and proteonomic profiling were not available at that time and still are not widely applied for this purpose.[36]

As reflected in this section and in the decision trees provided by FDA, the existence of large knowledge gaps, scientific uncertainties, and practical constraints led FDA to articulate a policy that provides a high degree of judgment and discretion on the part of producers when deciding how to demonstrate the GRAS status of novel varieties. Since that time, FDA has elaborated upon its "evolving approach" to GRAS determinations (for all foods and additives, not just GE), placing greater emphasis on independent determinations by producers (rather than positive affirmation of GRAS status by FDA), greater reliance on the "common knowledge" component and general scientific principles (rather than direct evidence from testing), a greatly limited use of public notice and comment procedures, and a more limited role for FDA in general.[37]

As noted, the granting of discretion to producers in performing independent GRAS determinations for GE foods was purposely designed into the 1992 policy because of legal ambiguities; that is, GE foods do not fit neatly into either the food additive or the adulteration category. Most of the branches in FDA's decision trees end in the advice that producers should voluntarily "consult FDA," as in the above excerpt. This provides flexibility for industry and FDA, but creates problems related to transparency, such that the scientific basis and evidence for GRAS determinations by industry are not readily available to members of the public or to the scientific community. The NRC (2000) committee stated:

> The details of these consultations are not readily available for public scrutiny. If the public wants to obtain documents containing information and data submitted to FDA for consultation, they must request the documents from FDA through the Free-

> dom of Information Act (FOIA). Processing and fulfilling FOIA requests can take a long time."[38]

More recently, FDA has begun posting summaries from these consultations on their website, but FOIA requests are still required to obtain more detailed data. An analysis of data from both sources conducted by a consumer interest group revealed a large number of gaps, errors, and inconsistencies in the material presented to FDA by developers.[39]

Allergens

FDA's 1992 policy states:

> FDA's principal concern regarding allergenicity is that proteins transferred from one food source to another, as is possible with rDNA and protoplast fusion techniques, might confer on food from the host plant the allergenic properties of food from the donor plant.[23]

It notes that while all known allergens are proteins, only a small fraction of the thousands of proteins in the diet have been found to be allergenic, with the most common ones being milk, eggs, fish, crustaceans, mollusks, tree nuts, wheat, and legumes (notably peanuts and soybeans). In some cases the specific protein in an allergenic food is known and in other cases it is not yet known. In either case, FDA states that "appropriate in vitro and in vivo allergenicity testing may reveal whether the new variety elicits an allergenic response in the potentially sensitive population."[23]

This guidance suggests that in vivo and in vitro methods may be capable of testing new varieties for allergenicity in those cases in which the foods or their allergenic proteins are already known, and FDA's decision trees guide producers in ascertaining which new varieties may warrant such testing. If new varieties are found to be allergenic, such foods could be labeled as such and/or steps could be taken to eliminate the allergenicity through more refined breeding. However, the methods for assessing the allergenicity of new proteins are indirect and indicative rather than conclusive,[40] as illustrated by the difficulties confronting the US Environmental Protection Agency's (EPA's) intensive examination of the CRY9C protein contained in StarLink corn.[41]

Although FDA's statement of policy is primarily concerned with the eight food types that account for 90% of known allergens, it is estimated that the remaining 10% of known allergens are distributed across at least 160 foods,[28] and many more may exist but have not yet been documented. Allergic reactions of varying severity to foods or food components are estimated to occur in 1% to 2% of adults and 5% to 8% of children.[42] Insomuch as transgenic techniques are uniquely capable of creating new varieties from vastly different genera of plants and animals, this widespread distribution of allergens introduces far greater uncertainties and the potential for introducing new allergens into widely consumed foods compared with other breeding methods. This was acknowledged in FDA's proposed rules in 2001,[30] but was not acknowledged in its 1992 policy statement. Instead, the 1992 policy statement simply acknowledged the problem but offered no guidance on how to resolve it:

> [In contrast to the case of known allergens,] a separate issue is whether any new protein in food has the potential to be allergenic to a segment of the population. At this time, FDA is unaware of any practical method to predict or assess the potential for new proteins in food to induce allergenicity and requests comments on this issue."[23]

It is unclear what guidance FDA could provide through those consultations other than that provided in the policy statement itself.

Context

A variety of contextual factors raise concerns regarding the level of safety assurance provided by FDA's policy. For instance, cultural norms and practices related to food selection (definitions of edible vs. nonedible portions of the plant), processing (storage, soaking, drying), preparation (cooking), and consumption vary widely within the United States and across cultures, but these differences are not well addressed in the policy statement. This is indicated by the heavy reliance on terms such as "typical methods of processing," "long history of use," and "normal diets," with an apparent US referent in mind.

An example of the weak treatment of contextual factors relates to the safety of transgenic foods for populations in developing countries. As early as 1986, the international (trade) dimensions were recognized in the Coordinated Framework for Regulation of Biotechnology,[27] which set the stage for FDA, the EPA, and the US Department of Agriculture (USDA) to develop their regulations in a coordinated fashion. However, the failure of FDA's policy to consider the international context from a consumer perspective is seen in the section "Issues Specific to Animal Feeds," where it is stated:

> Unlike a food in the human diet, an animal feed derived from a single plant may constitute a significant portion of the animal diet. For instance, 50 to 75 percent of the diet of most domestic animals consists of field corn. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet.[23]

The majority of people in developing countries, especially the poor, subsist on diets with 50% to 75% of calories coming from a single staple food.[43] Moreover, such populations suffer from high levels of morbidity,

malnutrition, and compromised immune systems, and often are the intended beneficiaries of US food aid programs that use GE commodities such as corn and soy. These important contextual factors were not respected in FDA's 1992 statement of policy, in the reassurances provided to African countries and the food aid community during the recent crisis in southern Africa,[44] nor in the public statements made in connection with the lawsuit brought against the European Union (EU) by the United States.[45] In the latter case, a US trade representative was quoted as saying:

> [The] dangerous effect of the EU's moratorium became evident last fall, when some famine-stricken African countries refused U.S. food aid because of fabricated fears – stoked by irresponsible rhetoric – about food safety. . . . Overwhelming scientific research shows that biotech foods are safe and healthy – a conclusion that the EU's own Directorate-General for Research reached two years ago.[45]

CONCLUSIONS

This analysis of FDA's policy reveals that efforts to ensure the safety of new varieties of plants are constrained by uncertainties, gaps in knowledge and methods, contextual factors, and practical considerations. These include the following:

- The list of potentially toxic substances in specific varieties of food crops, whose levels may be affected by rDNA insertions, is not known.
- Levels of known toxicants in foods vary widely for genetic and environmental reasons, and the "safe" or acceptable ranges are not known for most of them.
- The sensitivity and specificity of "taste tests" and other indirect tests for predicting the level or safety of toxicants in food is unknown, yet such tests are suggested as a possible screen for toxicants.
- Food allergens are known to be distributed across many foods, far beyond the eight most common ones, and to affect a significant proportion of adults (1%–2%) and children (5%–8%). Inasmuch as rDNA techniques are uniquely capable of transferring genes across vastly different genera and no practical methods exist for testing for new allergens, this appears to create a plausible risk from new allergens but one whose extent and seriousness is largely unknown and for which no tests presently are available.
- The FDA policy assumes that the nature, extent, and frequency of metabolic disruptions, activation and/or overexpression of target and non-target genes resulting from the (semi-random, tandem, and multiple-copy) insertion of new regulatory regions and structural genes is comparable to that from other breeding methods.

Based on this analysis of the 1992 FDA policy, Table 2 represents a judgment concerning the effectiveness of FDA's guidance to industry with respect to various categories of concerns. For reasons identified above, this guidance is likely to be partially effective with respect to known allergens and known toxicants.

Table 2. Effectiveness of FDA Regulations for Addressing Various Categories of Concerns in Transgenic Plants*

Source of Concern	Known† Toxicants	Known Allergens	Unknown Toxicants	Unknown Allergens
Intended Effects of the Transgene			Taste, oral toxicity	• Amino acid sequence • Digestibility • Heat resistance
Post-transcription modification	NA‡	NA	Taste, gross morphology	NM§
Pleiotropic effects of the transgene	NA	NA	Taste, gross morphology	NM
Insertional effects (location, multiple copies)	NA	NA	Taste, gross morphology	NM
Effects of regulatory regions (over-expression, activation)	NA	NA	Taste, gross morphology	NM
Effects of the genomic background	NA	NA	Taste, gross morphology	NM

*Dark shading = effective; light shading = partially effective; no shading = not effective.
†"Known" refers to knowledge of the identity, effective testing methods, "safe" or acceptable ranges and effects of processing methods.
‡NA = Not addressed.
§NM = No methods.

However, this table suggests that it is ineffective for detecting and preventing exposure to novel allergens and toxicants and to known allergens and toxicants that arise unexpectedly from various genetic or metabolic disruptions. Recent reviews reach similar conclusions,[46,47] and one of these calls into question the effectiveness of FDA's guidance even for known toxicants and allergens.[46]

It is important to note that FDA's policy statement does not include a clear or concise summary of the type shown in Table 2. To the contrary, the patterns and gaps depicted in this table are obscured in the policy statement by frequent references to: a) well-accepted methods that plant breeders use (such as backcrossing and inspection of gross agronomic characteristics) to eliminate undesired traits; b) the suggestion that many or all of the unexpected effects are just as likely with other methods of plant breeding (which has not been demonstrated); c) "practical constraints" that make it difficult or impossible to test for unexpected effects (which actually reflect large gaps in knowledge and testing methods); d) the assumption that long history of use of the donor and host plants ensures the safety of the new, transgenic varieties; and e) the suggestion that many or all of these unexpected effects are considered to be rare. Several of these claims are amenable to testing through scientific procedures, but no such evidence is provided or cited in the policy statement.

This analysis reveals that FDA's 1992 policy statement cannot be understood or justified only by reference to scientific evidence, knowledge, principles, and logic. Scientific principles in this case were adequate to indicate the plausibility of unintended consequences due to pleiotropy and insertional mutagenesis, but scientific knowledge and evidence were not adequate to indicate whether this was more or less likely or serious with genetic engineering compared with other breeding techniques. Similarly, the limited methods available for screening and testing GE foods can be traced to limitations in scientific knowledge. Science, by itself, cannot determine the most appropriate policy course in such situations.

Faced with these gaps in scientific knowledge and testing methods, the basic options available to FDA (from most restrictive to most permissive) were: a) to prohibit the marketing of GE foods until more evidence and testing methods became available; b) to require each producer to file a food additive petition, which would have the same effect as a prohibition because of the legal requirement to provide extensive scientific evidence demonstrating "reasonable certainty of no harm" in relation to "direct and indirect" effects; c) require or encourage producers to apply a feasible set of premarketing tests and precautions (focusing on known toxicants and allergens) while treating any unintended consequences under the post-market adulteration clause, which is consistent with the policy for other whole foods; or d) treat GE foods entirely through the post-market adulteration clause in the same manner as whole foods produced through all other breeding techniques. As noted, the FDA policy most resembles the third option, fundamentally representing a policy choice based on a variety of legal, economic, and political considerations rather than a choice dictated or supported by scientific considerations or public health protection alone. The nature of these other considerations, and the ways in which they interacted with scientific issues and institutions, are taken up elsewhere (Pelletier D, 2005[22] and Pelletier D, unpublished data, 2005).

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