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Science, Law, and Politics in FDA's Genetically Engineered Foods Policy: Scientific Concerns and Uncertainties

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The Food and Drug Administration's (FDA's) 1992 policy statement granted genetically engineered foods presumptive GRAS (generally recognized as safe) status. Since then, divergent views have been expressed concerning the scientific support for this policy. This paper examines four sources to better understand the basis for these claims: 1) internal FDA correspondence; 2) reports from the National Academy of Sciences; 3) research funded by US Department of Agriculture from 1981 to 2002; and 4) FDA's proposed rules issued in 2001. These sources reveal that little research has been conducted on unintended compositional changes from genetic engineering. Profiling techniques now make this feasible, but the new debate centers on the functional meaning of compositional changes.

Key words: unintended effects, scientific evidence, substantial equivalence

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INTRODUCTION

A recent paper[1] documented that the Food and Drug Administration (FDA) developed its 1992 Statement of Policy regarding genetically engineered (GE) foods in the face of significant scientific uncertainties concerning: a) the likelihood of unintended toxicants or allergens occurring in GE foods, b) whether GE foods are any different from conventional foods in this regard, and c) methods for testing GE foods. Although FDA acknowledged these issues, it granted GE foods the presumption of being GRAS (generally regarded as safe), in keeping with the legal status of conventional foods, while urging developers of GE foods to engage in voluntary premarket consultations.

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FDA justified its policy on the basis of legal considerations and several scientific claims or assumptions: a) genetic engineering is an extension of traditional plant breeding methods; b) unintended changes are possible with all breeding methods; c) plant breeders have established practices for detecting and screening out such changes, and d) existing food safety statutes are adequate for ensuring the safety of GE foods (notably the adulteration clause, in which unintended hazards are to be detected post-marketing).

FDA's policy has been interpreted and represented in strikingly different ways by various groups. One view, as expressed by FDA, the US Department of Agriculture (USDA), and a large number of scientific, professional, academic, and industry organizations, characterizes FDA's policy as being based on sound science, involving rigorous testing and being more demanding than that required for any other foods.[2-5] Moreover, the safety of GE foods is said to be indicated by extensive scientific research and the fact that no evidence of harm has been documented from GE foods currently on the market.

Another view, expressed by various non-profit organizations, scientific organizations, and some European governments, is that the FDA policy is based on very little scientific evidence regarding safety, and that the testing methods recommended by FDA are not adequate for ensuring safety.[6-11]

In light of these strikingly divergent interpretations and representations of FDA's policy, this paper examines four sources of information to better understand the nature and extent of scientific support for or against FDA's policy: 1) the views of FDA scientists and administrators who commented on FDA's policy when it was being drafted; 2) the views expressed in various reports from the National Research Council (NRC) and the National Academy of Sciences (NAS); 3) the types of publicly funded research supported through USDA from 1980 to 2002; and 4) the views expressed by FDA in 2001 when it proposed a stricter set of regulations for bioengineered foods.

Together, these sources confirm that a scientific basis does exist for expecting that GE could create food

safety problems and that current testing methods are inadequate in several important respects. The information presented here further suggests that little or no publicly funded research on these issues has been conducted in the decade before or after FDA's policy was issued. Despite this dearth of empirical research, the strongly supportive stance of the NAS, NRC, many scientific organizations, and industry created the appearance of a scientific consensus concerning the safety of GE foods. From a legal perspective, this apparent consensus was necessary for FDA to grant GE foods the presumption of being GRAS, for defending its policy in subsequent communications with the public, and for mounting a successful legal defense in subsequent litigation.[12]

INTERNAL FDA CORRESPONDENCE

As noted, FDA's 1992 policy is predicated on several key claims, assumptions, and conclusions. These include: a) rDNA techniques are an extension of other breeding techniques and pose no new or fundamentally different risks; b) therefore, regulation and testing should be based on the characteristics of the product rather than the process by which it was produced; c) procedures developed by conventional plant breeders for screening out unexpected and undesirable traits (morphological inspection, taste-testing, backcrossing, etc.) can be applied equally well to products from rDNA breeding to assess and ensure comparable safety; and d) in most cases, it is neither possible nor necessary to perform pre-market testing for unexpected toxic or allergenic changes, nor to conduct whole-animal feeding studies.

In legal terms, FDA's 1992 Statement of Policy is an *interpretation* of how *existing* regulations would be applied to GE foods, as opposed to being a new set of regulations. As such, the draft policy statement was not subjected to advance publication in the *Federal Register* and the Notice and Comment provisions normally associated with new regulations. This is important in the present case, because one of the functions of such procedures is to reveal the nature and extent of scientific agreement, disagreement, and evidence concerning the issue being considered by FDA.

In the absence of such information, it is instructive to examine some of the comments FDA received on its draft policy from some of its own scientists and administrators. This is possible in this case because of a lawsuit brought against FDA by a non-profit organization.[13] As a result of this lawsuit, over 44,000 pages of internal FDA memos, correspondence with other government offices, and supporting documents have been made public. Table 1 contains selected excerpts from this source bearing on some of the scientific questions confronted by FDA. A further compilation is available at the nonprofit's website (http://www.bio-integrity.org/), and the larger set of court documents is available at the National Records Center in Washington, DC.

The statements in Table 1, and the larger set available on the Bio-Integrity website, suggest that the 1992 policy departed in significant ways from scientific knowledge and principles, at least as viewed by some FDA scientists and senior administrators with long experience in the agency. However, in its legal defense FDA dismissed these criticisms, saying:

> *". . .plaintiffs have distorted the statements of these agency employees, taken most of them out of context, ignored contrary material in the same presentation – often on the same page . . . and ignored the fact that many of these comments pertained to an earlier draft of the Policy Statement and were substantively addressed in the final Policy Statement."*

FDA further asserts that "the Statement of Policy is based on a thorough review of the relevant scientific material and is reasonable and should be accorded deference [by the court, in keeping with administrative law and substantial case precedent]."[13]: defendants reply to plaintiffs memorandum, July 12, 1999, p. 12).

As part of the present research, the documents cited by FDA in support of its above claims were examined at the National Records Center. This review confirmed that FDA did undertake a thorough review of scientific material, but the cited material did not include any scientific evidence regarding the key concerns raised by the FDA employees. Specifically, these materials do not provide evidence on whether genetic and compositional changes induced by GE are more likely, or different in character, than those induced by conventional breeding. Moreover, a careful reading reveals that, contrary to FDA's assertion, these changes were *not* substantively addressed in the final policy statement.

As described below, scientific evidence regarding these concerns also is lacking in several reports from the NAS, the NRC, and the USDA research database.

NAS CONTRIBUTIONS

FDA's official policy, as with all regulatory policies, must respond to a variety of political, economic, legal, and administrative considerations in addition to scientific issues. By only reading the 1992 policy statement, it is difficult to determine which of these factors may have motivated FDA's various interpretations and decisions. Thus, a series of publications from the NAS and committee reports from the NRC (the working arm of the NAS) were analyzed as a quasi-independent assessment

Table 1. Comments of FDA Scientists and Scientific Administrators on the Draft 1992 Policy Statement on GE Foods

". . . the document is trying to force an ultimate conclusion that there is no difference between foods modified by genetic engineering and foods modified by traditional breeding practices. This is because of the mandate to regulate the product, not the process. . . . The processes of genetic engineering and traditional breeding are different, and according to the technical experts in the agency, they lead to different risks. There is no data that addresses the relative magnitude of the risks . . . the acknowledgement that the risks are different is lost in the attempt to hold to the doctrine that the product and not the process is regulated." (January 8, 1992 memo from Linda Kahl, FDA Compliance Officer)
"What has happened to the scientific elements of this document? . . . The unintended effects cannot be written off so easily by just implying that they too occur in traditional breeding. There is a profound difference between the types of unexpected effects from traditional breeding and genetic engineering which is just glanced over in this document. . . . The potential for activating cryptic pathways has *NOT* 'been effectively managed in the past by sound agricultural practices,' because the breeders have not had to face the issue of new, powerful regulatory elements being randomly inserted into the genome. . . . It is not prudent to rely on plant breeders always finding these types of changes (especially when they are under pressure to get the product out). Nowhere is such an issue discussed or examined in this document." (March 6, 1992 memo from Dr. Louis Pribyl, FDA microbiologist)
"Pleiotropic effects occur in genetically engineered plants obtained with *Agrobacterium*-medium transformation at frequencies up to 30% (Ref.). Most of these effects can be managed by the subsequent breeding and selection procedures. Nevertheless, some undesirable effects such as increased levels of known naturally occurring toxicants, appearance of new, not previously identified toxicants, increased capability of concentrating toxic substances from the environment (e.g., pesticides or heavy metals), and undesirable alterations in the levels of nutrients may escape breeders' attention unless genetically engineered plants are evaluated specifically for these changes." (November 1, 1991 joint memo from the Division of Food Chemistry and Technology and the Division of Contaminants Chemistry, in the form of suggested language for the "Points to Consider" portion of FDA's draft 1992 policy)
"In response to your question on how the agency should regulate genetically modified food plants, I and other scientists at CVM have concluded that there is ample scientific justification to support a pre-market review of these products . . . Generally, I would urge you to eliminate statements that suggest that the lack of information can be used as evidence for no regulatory concerns." (February 5, 1992 memo from Dr. Gerald Guest, Director of FDA's Center for Veterinary Medicine).

Source: Internal FDA correspondence released in Bio-Integrity vs. Shalala (1998). Further details available at www.bio-integrity.org.

of the scientific and regulatory issues regarding GE foods. Although there is a substantial body of literature documenting the ways in which expert bodies themselves are influenced by extra-scientific considerations,[14-17] it is assumed here that the NAS deliberations and judgments should be less directly affected by political, economic, legal, and administrative considerations and more inclined to focus on scientific evidence bearing on safety.

Pre-1992

During the period 1984–1989, when federal biotechnology regulations were still evolving, the NAS published three NRC committee reports focusing on biotechnology,[18-20] one influential white paper,[21] one convocation report,[22] and one symposium report.[23] These six publications were reviewed to ascertain the nature of any safety and regulatory concerns raised in relation to GE foods, and the nature of the research cited and/or recommended for addressing those concerns. The overwhelming focus in four of these six reports was on the potential benefits of agricultural and microbial biotechnology, identification of promising or priority research questions, issues related to scientific training, funding, university-industry relations, and other institutional matters.[18,19,22,23] Microbial and/or environmental safety was the focus of four pages in the 1984 report[22] (out of 76 pages), received no attention in the 1985 report[18] (out of 117 pages), and occupied four pages in the 1987 NRC report[19] (out of 224 pages). It was the exclusive focus of the 1987 NAS white paper[21] (24 pages) and the 1989 NRC report[24] (170 pages), because these latter two reports were commissioned in response to the increasingly urgent need for federal agencies to clarify safety issues and regulatory frameworks. None of

these five reports preceding the development of FDA's 1992 policy devoted any attention to potential food safety concerns.

The one NAS publication that did address food safety concerns was neither a committee report nor an official statement of the NAS. Rather, it was a compilation of papers from the Food and Nutrition Board's annual symposium.[23] This symposium included presentations by five speakers, one of whom focused on potential food safety problems.[25] As noted by this speaker, in 1973, an NRC Task Force on Genetic Alterations in Food and Feed Crops had taken a prescient view of the potential food safety and nutritional concerns associated with genetic alteration through classical breeding. Their report stated:

> There is an urgent need for expert groups competent in nutrition and toxicology to develop guidelines which will indicate to plant breeders those changes in chemical composition of plants used for food or feed which are desirable, undesirable or of no practical significance. These guidelines will need to be developed for each of the major food or feed crops since the relative biological significance of chemical changes will vary from one to another. For some nutrients, and many potentially toxic substances, there is insufficient information available to establish reliable goals or limits and analytical methods are often inadequate for their implementation.[26]

Reflecting back on this in 1988, Doyle notes that the Task Force's recommendations were not acted upon due to lack of funds and because the focus of the report was on plant breeding and not biotechnology. He goes on to say, in 1988:

> Unfortunately, the situation hasn't changed in any of these data or analytical areas since this report was filed. But with biotechnology now upon us, the research called for by the 1973 Task Force is even more urgent than it was 14 years ago. Accordingly I would urge the Academy to revisit this issue very soon, and consider launching a major review in this area.[25]

As described below, an NRC committee writing in 2000 and an Institute of Medicine (IOM) committee writing in 2004 both were to discover that the situation still had not changed by that date and both made the same types of recommendations.[27,28]

From this review, it appears that the NAS publications in the early/mid 1980s were primarily focused on identifying the scientific and institutional requirements for bringing to fruition the promising applications of biotechnology. The focus of NAS publications changed dramatically in the 1987 white paper and the 1989 report, which were written specifically to assist the regulatory agencies that were having difficulty reaching consensus on some key issues.

The 1987 white paper, which was the product of a five-member panel (rather than a formal committee), articulated three key conclusions pertaining to the introduction of rDNA-engineered organisms into the environment:

1) There is no evidence that unique hazards exist either in the use of rDNA techniques or in the transfer of genes between unrelated organisms;
2) The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; and
3) Safety assessment of rDNA organisms should be based on the nature of the organisms and the environment into which it will be introduced, not on the method by which it was modified (i.e., characteristics of the product, not the process).

It is important to note that these principles were developed specifically to guide regulations related to the introduction of GE microbes and plants into the environment. No attention was given to food safety concerns in these reports, nor to the possibility that they may differ in character from environmental concerns. However, these principles, and a variety of conclusions that flow from them, have since been widely cited as authoritative scientific support for FDA's approach to food safety assessment. For instance, the expert committee convened by the Institute of Food Technologists[2] (IFT) identified 11 previous expert committees that have repeated and reaffirmed these principles emanating from the 1987 NAS white paper. Although the 1987 white paper only addressed issues related to introductions into the environment, this endorsement of the NAS principles is cited as evidence (by IFT and other organizations) of a broad scientific consensus related to food safety. This is despite the fact that FDA's 1992 policy statement (and other sources reviewed below) acknowledges concerns related to insertional mutagenesis and pleiotropy and that these cannot be detected reliably through currently available testing methods.

Post-1992

The first detailed NAS examination of potential food safety concerns related to GE foods was commissioned in 2000, when a review of the science and regulation of pest-protected plants was undertaken.[27] This review was commissioned largely in response to the intense public controversy concerning GE foods that began in the mid-

1990s, and in response to requests from several professional societies, members of Congress, and other groups desiring an impartial review. Given the short time frame for the review (approximately one year), the committee restricted its attention to genetically modified, pest-protected plants, drawing heavily upon experience with the *Bacillus thuringiensis* (Bt) crops in commerce up to that time. The committee examined issues related to the environment and human health, but the present paper only draws upon its findings and recommendations pertaining to human health.

As shown in Table 2, the NRC report[27] provided three recommendations in the executive summary in relation to human health. Two of these (numbers one and two) identify issues for further research related to toxins, and one is a common statement of reassurance based on the lack of evidence of safety problems for GE foods currently on the market. Four additional recommendations are provided in the text of the report, but were not included in the executive summary. One of these (number four) urges more rigorous testing for toxicity and allergenicity than is suggested by the 1992 FDA policy; another (number five) recommends that FDA provide better preliminary guidance for allergenicity testing; another (number six) recommends research to develop more direct and reliable methods to test for allergenicity; and one (number seven) concludes that current toxicity and allergenicity testing protocols are currently appropriate "inasmuch as the testing protocols are the ones currently available." This latter conclusion is drawn despite the concerns implied in the other recommendations and stated elsewhere in the report.

In contrast to the more circumspect tone of the official recommendations, the text of the NRC report[27] is more candid about the potential for unintended effects arising from rDNA and more critical in its assessment of current testing protocols (Table 3). However, as with the 1992 FDA policy, the NRC report[27] frequently tempers these concerns by claiming that unintended effects from transgenic breeding may be just as likely to occur in conventional breeding. Neither the FDA policy statement nor the NRC report[27] present evidence to support this claim, and a later IOM report came to the opposite conclusion.[28]

Taken together, the text of the NRC report[27] identifies numerous areas of concern, and the official recommendations confirm this implicitly by urging research, development, and application of improved methods to improve testing protocols. However, the official NRC recommendations stop short of concluding that current testing procedures are inadequate; instead, they provide reassurance concerning the presumed safety of marketed GE foods. They do so by deliberately conflating "no evidence of harm" with "evidence of no harm." Moreover, they conclude that current testing is "currently appropriate" on the rather narrow and questionable basis that these are the only protocols currently available. The latter is a statement regarding a practical constraint rather than a statement regarding the adequacy of current protocols for protecting public health or for meeting the legal standards required for demonstrating GRAS status.

Table 2. Official Recommendations Related to the Human Health Implications of Genetically Modified Pest-Protected Plants (NRC 2000)

1. Research, Toxins: "Assess and enhance data on the baseline concentrations of plant compounds of potential dietary or other toxicological concern, and determine how concentrations of these compounds may vary depending on the genetic background of the plant and environmental conditions." (p. 8, Executive Summary)
2. Research, Toxicity: "Examine whether longterm feeding of transgenic pest-protected plants to animals whose natural diets consist of the quantities and type of plant material being tested (for example, grain or forage crops fed to livestock) could be a useful method for assessing potential health impacts." (p. 9, Executive Summary)
3. Conclusion: "In conclusion, although there is the potential for the adverse health effects discussed in this section, the committee is not aware of any evidence that foods on the market are unsafe to eat as a result of genetic modification." (p. 9, Executive Summary)
4. Regulation, Testing: "When the active ingredient of a transgenic pest-protected plant is a protein and when health effects data are required, both short term oral toxicity and potential for allergenicity should be tested. Additional categories of health effects testing . . . should not be required unless justified." (p. 73)
5. Regulation, Allergens: "FDA should put a high priority on finalizing and releasing preliminary guidance on the assessment of potential food allergens, while cautioning that further research is needed in this area." (p. 168)
6. Research, Allergens: "Priority should be given to the development of improved methods for identifying potential allergens in pest-protected plants, specifically, the development of tests with human immune system endpoints and of more reliable animal models." (p. 73)
7. Regulation, Testing: "When the active ingredient is a protein, short-term oral toxicity and potential allergenicity testing are currently appropriate, inasmuch as the testing protocols are the ones currently available." (p. 73)

Table 3. Concerns Related to Safety Testing of Genetically Modified Pest-Protected Plants (NRC 2000, quotations taken from text of the report)

1. "In the regulation of [Bt crops], the emphasis has not been on detailed assessments of safety for humans or domestic animals. Rather, it has been on explaining the scientific basis for why there is probably no appreciable risk and justifying the tests which are required." (p. 64)
2. ". . . [A]llergenicity is assumed to be unimportant for many Bt endotoxins, more because of the common characteristics of food allergens than because of rigorous testing." (p. 66)
3. "Post-transcriptional modification is known to occur in plants and such characteristics as the degree of glycosylation might also affect stability and other physicochemical properties of proteins. Tests should preferably be conducted with the protein as produced in the plant." (p. 66)
4. "Although the standard tests indicate non-allergenicity for Cry3A, they were not carried out on the endotoxin produced in potatoes, and none involved testing the immune system itself." (p. 66)
5. "In general, oral toxicity testing for Bt endotoxins is based on the presumption that there is unlikely to be a problem inasmuch as a number of Bt toxins have been widely used for many years in microbial sprays without human toxicity." (p. 65)
6. ". . . [M]ost previous field uses resulted in minimal toxin ingestion by humans because sprayed microbial Bt toxin only remains effective for an average of 1.5 days. Also, sprayed microbial Bt toxins are protoxins, while some Bt plants produce activated toxins." (p. 65)
7. "Tiered tests involving protein homology and stability comparisons with known food allergens and immunoassays for specific classes of antibodies are also proposed in these documents . . . and are currently used by the agencies as a screen for allergenicity." (p. 67)
8. "However, [the recommended tests] either are indirect, do not involve adverse effects or are otherwise problematic for testing of novel proteins that have not previously been components of the food supply." (p. 67)
9. "Another problem of potential importance, the appearance of toxins that were not present in the parental lines, also has been demonstrated in potato [the steroidal alkaloid demissine]." (p. 71)
10. "Monitoring for pleiotropic effects should be an important element of health-safety reviews, in addition to the testing of introduced gene products; there is a lack of an extensive database on the natural levels of such compounds." (p. 8)
11. "Most toxicity testing is conducted using the purified plant-pesticide and, therefore, pleiotropic effects of the genetic modification cannot be monitored. If proper controls are used, feeding whole plants to test animals might allow for the detection of potential toxicity due to pleiotropic effects." (p. 70)
12. "The 'edible' portion of a plant varies with the species and the consumer in question. In the human diet, the part eaten can also vary with the cultural background of the consumer." (p. 72)

FEDERALLY FUNDED RESEARCH ON PLANT SYSTEMS AND FOOD SAFETY

Prudent decisions regarding the regulation of new technologies requires knowledge not only of the potential benefits of new technologies (as promoted by the NRC and others prior to 1992), but also scientific knowledge of the potential risks and means for mitigating such risks. Thus, it is of interest to examine the extent to which these subjects were addressed in federally funded research during the 1980s, when gene transfer technologies and early GE foods were being developed, as well as in the 1990s, when the public controversy erupted and key scientific uncertainties became more widely recognized.

An overall sense of the research investment related to plant systems research (including food safety) during the 1980s can be obtained from data in a USDA report published in 1993.[29] Government-sponsored agricultural research includes USDA's intramural component administered through the Agricultural Research Service (ARS) and a university-based component administered through the Cooperative State Research Service (CSRS). Universities in that latter system also obtain funds from their respective state governments as well as from other federal and non-federal sources, such that USDA's contribution to the university system comprised only about 19% in 1991. It is not possible to obtain a complete accounting of food safety research across all components of the ARS/CSRS system during the 1980s, so a series of partial comparisons are provided below.

Table 4 shows that total university funding (from all sources) for research related to plant systems increased by 24% from 1981 to 1991 (from $417.6 million to $516.7 million). Funding for research related to plant production, plant/environment, and plant protection makes up the vast majority of plant systems research, and these three categories increased 9%, 47% and 24%, respectively, during the decade. By contrast, funding for research on plant food safety represented only 2.3% of the total in 1981, and declined to 1.3% of the total in

Table 4. University Research in the Plant Systems Category, 1981–1991*

Research Problem Area	1981		1991		
	$ (millions)	%	$ (millions)	%	Change
Plants/Production	166.4	40	182.0	35.2	+9%
Plants/Protection	127.8	31.6	158.2	30.6	+24
Plants/Environment	41.4	9.9	61.0	11.8	+47
Plants/Safety	9.7	2.3	6.9	1.3	−29%
Other	72.3	17.3	108.6	21.0	+50%
Totals	417.6	100.0	516.7	100.0	+24%

*Figures adjusted for inflation. Values include research funded from USDA, state, other federal and non-federal sources.

1991, a 29% decrease. As expected, funding for molecular biology increased dramatically, from $6 million to $45 million, representing a 625% increase during the decade.

Only limited comparisons are available for the ARS (intramural) portion of USDA's research portfolio and for the portfolio as a whole. The USDA report notes that total funding by USDA for all food safety research (animal and plant) increased 13% over the decade, from $37.3 million to $42.1 million (inflation adjusted). Whereas USDA (CSRS) funding of university research on food safety showed steady growth during the decade, USDA funding for its own intramural research on food safety was erratic, showing declines in 1985 and 1987 before increasing again in 1989. These figures represent all categories of food safety research, including animal and plant systems, pre- and post-harvest/slaughter. Although no quantitative breakdowns are provided, the report states:

> The category . . . receiving the greatest commitment of scientist years (SYs) and dollars was disease agents, followed by chemical residues. Categories receiving significantly less SYs and dollars were, in descending order, mycotoxins, naturally occurring toxicants and environmental contaminants. . . . About two-thirds of the projects and expenditures and three-quarters of the SYs were aimed at avoiding, controlling, and detecting food safety hazards after harvest or slaughter.[29]

The USDA report does not indicate what portion, if any, of the food safety research during the decade may have been focused specifically on the safety of GE plants. However, in a section on "Emerging Issues" it states:

> As food crops requiring fewer chemicals are developed, research data will be required to ensure that these crops are not replacing human-made pesticides with toxic natural pesticides. . . . Research on the safety of foods produced through biotechnology also is essential to ensure consumer acceptance of biotechnology as a tool in food production and manufacturing. Scientists must be vigilant in assessing the complex interactions of food components as they relate to health, particularly as 'designer foods' become more common.[29]

This was written one year after FDA had issued its 1992 policy, but from the funding patterns it appears that these issues did not receive attention in time to support the development of the FDA policy.

Much greater detail is available concerning the research topics receiving attention after FDA's 1992 policy was issued, due to the fact that USDA made significant improvements to its Current Research Information System (CRIS). CRIS is a searchable, publicly accessible database containing the titles and descriptions of intramural and university research projects. Investigators are required to submit electronic reports each year and, although the database does not have complete coverage, its coverage has steadily improved since its inception in 1994 and now contains vast quantities of information.

Table 5 shows the number of research projects containing various combinations of search terms and key words from 1994 through 2002. Overall, this database contains 21,936 projects related to plants (row a), of which 3041 also deal with biotechnology or transgenics (row b), 682 deal with toxins (row c), and 67 deal with allergens (row d). Of the 3041 projects dealing with plant biotechnology, 145 are related to toxins in some way (row e) and 19 are related to allergens (row f). Project descriptions in these latter categories were inspected individually to better characterize the focus of these studies. This revealed that two of the toxin studies and five of the allergen studies were specifically using transgenic methods to study or alter known toxins, allergens, or allergenic foods. None of the toxin-related projects was designed to study unintended toxins in GE foods. Two projects, one beginning in 2001 and one ending in 2001, sought to develop an animal model to test for unexpected allergens in GE foods. Thus, based on this extensive CRIS database, it does not appear that the

Table 5. Number of USDA-Funded Research Projects on Selected Topics, 1994–2002 (Source: USDA CRIS database: *http://cristel.nal.usda.gov/star/system.html*)*

Search String	1994	1995	1996	1997	1998	1999	2000	2001	2002	Totals
a) Plant†	60	241	492	2122	1087	2576	2650	3132	9576	21,936
b) Plant + Biotech‡	9	42	73	198	194	327	356	502	1340	3041
c) Plant + Toxin	1	9	21	36	37	72	77	108	322	682
d) Plant + Allergen	0	1	1	5	0	2	7	14	37	67
e) Plant + Biotech + Toxin	0	1	4	8	8	13	17	24	70	145§
f) Plant + Biotech + Allergen	0	0	0	1	0	0	1	4[4]	13	19‖

*Results are based on the CRIS database as accessed on 11/15/03. Searches a–d are based on Full Text search as described at the CRIS website. Searches e–f represent a subset of searches c–d, respectively, created by adding the terms "transgenic or biotechnology" to the key word field. "Totals" represent the sum of year-by-year counts as shown here.

†Search string included "plant" or "crop."

‡Search string included "biotechnology" or "transgenic."

§None of these projects sought to screen for unintended toxins in GE foods; most focused on toxins related to pest resistance or other production-related issues; two sought to reduce the levels of known toxicants using transgenic methods.

‖Two of these projects sought to develop an animal model to test for allergenicity of GE foods; others sought to characterize the levels of known allergens using transgenic methods, and five sought to lower the levels of such allergens using transgenic methods.

uncertainties plaguing FDA's 1992 policy have been taken up as significant focus for USDA-funded intramural or university-based research, despite the intense public controversy that began early in the period covered by this table.

Although the CRIS database does not achieve complete coverage (i.e., not all investigators submit reports each year), there is no reason to suspect a disproportionate underreporting of projects related to toxins and allergens in GE foods as opposed to other topics.

It is noteworthy that for about 10 years, USDA has funded a special research program to examine environmental and agricultural risks related to GE crops, the Biotechnology Risk Assessment Program. Although this program is funded at a very low level (about $1 million per year), there does not appear to be a similar program even of this size related to food safety or human health risks.

A similar analysis was undertaken based on searches in Medline, focusing on the refereed food safety literature.[30] That review documented a total of 101 food safety papers with the phrase "genetically engineered foods," representing 67 papers with the phrase "adverse effects of transgenic foods," and 44 papers with the phrase "toxicity of transgenic foods." Of these, only eight papers reported findings from original experimental studies of the safety of GE products, and all of these studies were in rodents. Most of the remaining papers offered opinions and commentaries on the safety of GE foods, but without offering supportive data. It is noteworthy that the committee conducting the 2000 NRC report[27] was able to identify and commented upon only one direct feeding study in a peer-reviewed journal, this being the disputed and highly controversial study of GE potatoes in rats.[31]

A review of the literature in 2000 documented a similar paucity of experimental evidence in relation to the ecological risks and benefits of GE crops,[32] and this was confirmed by an NRC committee[33] that identified a number of high-priority areas for biosafety research.

In response to the aforementioned NRC report on ecological risks,[33] an amendment was added to the National Science Foundation (NSF) authorization bill in the House of Representatives that same year to establish a $35 million program for fundamental research related to the environmental effects of genetically modified organisms (H.AMDT 501 to H.R.107-4664). The amendment was defeated 259 to 165, with Republican members voting 216 to 1 in opposition. The stated reason for the opposition is that such funding would "politicize scientific research" and that scientists alone should decide the most appropriate research agenda for the NSF. These reasons were cited despite the fact that committee debate on this amendment made it clear that these research needs were identified by an NRC committee, the operational arm of the body (the NAS) officially known as "advisors to the nation" on scientific matters.

CONCLUSIONS REGARDING FDA'S 1992 POLICY

This examination of FDA's 1992 policies regarding GE foods holds several lessons concerning the roles and uses of science in policy development. These lessons pertain most directly to the present case of GE foods, but also have relevance to the forthcoming nutritionally altered foods.

Many of the potential unintended consequences in the GE foods case were amenable to scientific investigation to characterize their plausibility and likelihood, frequency, severity, and/or possibilities for mitigation, but research on these issues in the GE foods case appears to have been sorely neglected, even in the USDA-funded

research portfolio. From a science policy perspective, the development of the mechanistic knowledge, methods, and tools for the investigation of unintended consequences may be a uniquely public sector responsibility because, absent regulatory requirements, the private sector has insufficient incentive to do so. However, the intramural and extramural research funded by USDA suggests that even in the public sector, the prevailing incentives only favored research to develop and apply the technology, rather than to investigate unintended consequences.

These gaps and biases in public research agendas resulted in scientific uncertainties that had a direct and profound impact on FDA's decision to adopt and justify policies that, from a legal perspective, treated GE foods no differently than conventional foods. Specifically:

- They permitted the default assumption to be made that unintended consequences appear no more likely in GE foods than in conventional foods, thereby allowing FDA to grant GE foods presumptive GRAS status.
- They limited the tools and methods available for pre-market testing of individual products and, therefore, limited the types of tests FDA could require of developers.
- They virtually required FDA to use only its post-market authority under the adulteration clause rather than pre-market testing.
- In the absence of positive evidence of unintended compositional changes and functional consequences, FDA was able to claim that there was no scientific basis for mandating the labeling of GE foods (though it could have required labeling on other grounds).

Despite the existence of critical gaps and uncertainties in scientific knowledge concerning unintended consequences, key scientific organizations (including but not limited to the various committees of the NAS as reviewed here) displayed overwhelming support for and promotion of biotechnology in general, including GE foods, while devoting little or no concerted investigation of potential food safety risks. Moreover, the NAS and NRC increasingly have been asked to render scientific judgments on issues with enormous implications for the regulation of GE foods, which has strained its ability to separate the scientific questions from the profound policy implications that loomed over the members of these committees. This is seen most clearly in the white paper from the five-member committee of the NAS Council[21] and in the report analyzed in detail in this paper.[27]

Examination of the two major regulatory options available to FDA (the food additive/GRAS category versus the adulteration category) highlights that the scientific uncertainties, gaps in knowledge, and supportive statements from influential scientific organizations do not fall "neutrally" upon FDA. As described in greater detail elsewhere,[12] FDA's decisions were circumscribed by some of its statutes and, more importantly, subject to high-level political pressure to minimize regulatory interference with this new industry. Within this larger political and legal context, the lack of an empirical understanding of the nature and extent of compositional changes arising from pleiotropic effects or insertional mutagenesis in GE versus conventional breeding, and the absence of any organized expression of concern from the scientific community, is what permitted FDA to exercise its discretion in favor of less-stringent regulations. The legal and political dimensions of this are examined in detail elsewhere.[12]

RECENT DEVELOPMENTS

While the primary focus of this paper has been on events surrounding the development of FDA's 1992 policy statement, a number of more recent developments shed light on the prospects for changes in this policy in the future.

FDA's 2001 Proposed Rules

In response to the intense public controversy over GE foods during the 1990s, FDA initiated a process to re-examine selected aspects of its 1992 policy. One part of this process was to convene three public meetings in different parts of the United States and request written comments on specific questions (in the process receiving over 35,000 comments). Subsequently, FDA issued the proposed rules in 2001 and provided several reasons for proposing premarket notification, when it had not deemed it necessary in 1992 (Table 6).

The justifications in Table 6 are significant because they overturn two of the fundamental principles expressed in the 1992 policy to argue that there was no scientific basis for specific regulations for GE foods, namely that there is no difference between GE foods and foods produced through traditional breeding and that the characteristics of the product, not the process, should determine the level of oversight. Although FDA indicates that the reason for urging greater oversight in 2001 is due to the greater scope and complexity of the genetic changes, the 1992 policy statement (and numerous NRC reports in the 1980s) clearly demonstrate that such changes were envisioned prior to the 1992 policy. A more plausible reason for FDA to reverse its earlier position relates to the intense public controversy in the late 1990s and the need to satisfy the public (as well as other governments) that the United States intended to exercise stronger oversight.

Table 6. FDA's Stated Reasons for Proposing Pre-market Notification in 2001

". . . rDNA technology greatly facilitates, relative to traditional breeding, both the introduction of specific new substances into the foods and the directed modification of the composition of foods. This is in part because the technology expands the range of sources of new substances that can be introduced into plants, relative to [traditional breeding]. . . . In addition, rDNA technology increases the speed by which traits can be introduced into food crops . . . . FDA expects that these techniques are likely to be utilized to an increasingly greater extent by plant breeders and that the products of this technology are likely in some cases to present more complex safety and regulatory issues than seen to date." (FDA 2001:4709)
". . . FDA recognizes that because breeders utilizing rDNA technology can introduce genetic material from a much wider range of sources than previously possible, there is a greater likelihood that the modified food will contain substances that are significantly different from, or are present in food at a significantly higher level than, counterpart substances historically consumed in food. In such circumstances, the new substances may not be GRAS and may require regulation as food additives." (66 FR 4709)
"FDA believes that in the future, plant breeders will use rDNA techniques to achieve more complicated compositional changes to food, sometimes introducing multiple genes residing on multiple vectors to generate new metabolic pathways. FDA expects that with the increased introduction of multiple genes, unintended effects may become more common. For example, rice modified to express pro-vitamin A was shown to exhibit increased concentrations of xanthophylls . . . and rice modified to reduce the concentration of a specific protein was found to exhibit an increased concentration of prolamine . . . ." (66 FR 4710)
"There is substantial basis to conclude . . . that there is greater potential for breeders, using rDNA technology, to develop and commercialize foods that are more likely to present legal status issues and thus require greater FDA scrutiny that those developed using traditional or other breeding techniques. (66 FR 4711)
"Intended changes to the composition or characteristics of the food also could raise safety questions about the food. For example, it is possible that a developer could modify corn so that the corn becomes a significant dietary source of the nutrient folic acid. Folic acid is used to fortify many foods, including breakfast cereals, because of the relationship [with] neural tube defects. However, excess folic acid in the diet can mask the signs of vitamin B12 deficiency. [In addition] it is possible that a modification would be intended to decrease the level of a substance that is considered undesirable, such as the phytate that naturally occurs in soybeans . . . or the fat content of a food." (66 FR 4721)

Taken at face value, FDA's proposed rules in 2001 signal a significant change in FDA's position concerning oversight of future GE foods. As of this writing, however, FDA has not finalized these rules and has indicated that it has no intention of doing so. One reason is that the concern about bioterrorism after the terrorist attacks in 2001 has re-ordered many of the food-related priorities of the agency. However, even in the absence of those events there have been continuing questions about the agency's legal authority to regulate GE foods differently than conventional foods (i.e., a "regulatory trigger"), given the lack of evidence that the process of genetic engineering does (or does not) warrant greater oversight.

This question of whether a special regulatory trigger should exist for GE foods has been at the center of the policy debate among the agencies since the mid-1980s. The next section highlights some more recent scientific understandings and potential testing methods bearing on this question, which could lend scientific support for a special regulatory trigger for GE foods and a more powerful set of methods for assessing substantial equivalence.

Evolving Science and Testing Methods

The regulatory trigger and pre-market assessment debate can be usefully separated into three distinct questions:

1) Does genetic engineering (as a class) induce compositional changes in food at a higher frequency/likelihood or with different consequences than conventional breeding?;
2) Does a particular GE food have substantial compositional changes compared with its non-GE counterparts?; and
3) Do the observed compositional changes in a particular GE food have potential adverse biological or health implications?

As noted, the long-standing concern over potential unintended compositional changes in GE foods has not stimulated a commensurate increase in federal funding for research on the likelihood or functional consequences of such changes. However, recent reviews have identified a small number of studies published after 1997 directly examining this possibility in GE foods.[34,35] These studies confirm that genetic engineering can in-

crease the levels of metabolites other than those directly related to the transgene. For instance, a study of several lines of transgenic potatoes with various modifications to sucrose metabolism documented that the transgenic varieties had distinct metabolite profiles (compared with non-GE counterparts grown under identical conditions) across the majority of the 88 metabolites examined, including the appearance of some novel metabolites.[36] However, neither this study nor those in Kuiper's review[34] address the question of health or functional consequences.

In addition to direct comparisons of GE foods with their non-GE counterparts, the regulatory trigger question is informed by an accumulating body of knowledge concerning the complex functional architecture of the genome and the extensive changes in gene expression that can arise from insertional mutagenesis.[37] For instance, a recent study of the genetic regulation of olfaction in *Drosophila* examined the extent of transcriptional perturbations from single P-element insertions in five of the eight loci forming an epistatic network.[38] The authors reported that a total of 530 genes were co-regulated (as defined by statistically significant differences in transcription) in response to single mutations at these five loci and concluded:

> The ability to analyze transcriptional profiles of entire genomes has transformed the traditional view of simple genetic pathways, in which a single mutation has a restricted effect on a specialized function, into a more complex concept of genetic networks. Single mutations in a defined genetic background can profoundly shift the landscape of epistatic interactions in such networks. The large numbers of coregulated genes for any one mutation implies extensive pleiotropy and indicated that any two wild-type strains may be different with respect to many transcripts.[38]

Thus, the evolving understanding of genomic architecture and the small number of studies directly comparing GE foods with their non-GE counterparts confirm that potentially widespread unintended effects can and do occur as a result of genetic engineering. A recent review has documented that this is the case with food crops, including many of those in commercial use.[6] However, it remains to be shown through the examination of a large number of genetic transformations whether the frequency, magnitude, or functional consequences of these effects are different from those seen with conventional breeding methods. A recent IOM committee has recognized this long-standing gap in knowledge and recommended an extensive program of research to address it.[28]

The other significant scientific advance since FDA's 1992 policy statement is in the expanded range of tools potentially available for broad-spectrum genomic, proteomic, and metabolite profiling of GE foods.[35,36,39-42] For policy purposes, such tools are important because they could help answer the first two questions posed above. The NAS[21] and the FDA[43] have previously asserted that no differences exist for genetic engineering as a class, but these tools now permit an empirical test of that assertion.[21,43] In addition, these tests allow case-by-case examination of a far wider range of compositional characteristics than the crude proximate analysis currently used in making that determination. This could lend greater meaning and credibility to the notion of "substantial equivalence" as a means for determining which specific GE foods may warrant more intensive premarket scrutiny and guide subsequent testing by revealing which specific compounds in those foods may have been unintentionally elevated, reduced, modified, or created.

IMPLICATIONS FOR NUTRITIONALLY ALTERED FOODS

One of the explanations advanced for public resistance to GE foods is that the first-generation crops possessed traits and benefits of primary interest to producers rather than consumers.[44,45] These authors further suggest that greater public support for GE foods will be forthcoming if and when consumers perceive some personal benefits from this technology, such as in nutritionally altered foods. To the extent that this prediction is accurate, it is likely to stimulate a significant expansion in the number, type, and complexity of genetic and compositional alterations in GE foods, including intended and unintended changes. FDA clearly anticipates this possibility, as shown in its proposed rules,[46] but as of this writing has made no changes to its 1992 policy.

It is in this context that the IOM report[28] is significant, especially its decision to not recommend (at this time) the use of profiling methods in premarket assessments of the composition of GE foods. Although the committee recommended a vigorous federal research agenda on these issues, the neglect of such research over the past two decades, as documented in this paper, and the current fiscal climate suggest that this is unlikely to occur. Of even greater importance, however, is that the biological and health effects of compositional changes are highly specific to each genetic transformation and need to be investigated on a case-by-case basis rather than as part of a more basic public research agenda. Thus, as a practical matter, the financial and legal responsibility for undertaking such product-specific safety research should properly rest with the producers of each GE food rather than with the federal government.

While most of this paper has focused on potential

risks caused by insertional mutagenesis and pleiotropy, and both of these will apply with equal or greater force to nutritionally altered foods, as acknowledged by FDA,[46] this discussion has largely ignored the policy implications of human genetic variation being brought to light by advances in human genomics. As this knowledge accumulates, specifically in relation to gene-toxin and gene-nutrient interaction, the regulation of nutritionally altered GE foods, food additives, dietary supplements, and conventional foods will become increasingly difficult. This is because such research may bring to light the existence of genetic subpopulations that respond differentially (in terms of risks or benefits) to various bioactive components in the food supply, thereby creating difficult tradeoffs for policy makers.

One current example of such tradeoffs relates to folate. Certain genotypes appear to have increased requirements for folate to avoid neural tube defects, but a national fortification policy to meet these needs may place large numbers of older adults at risk from undetected vitamin B_{12} deficiency and interfere with widely used medications.[47-49] A second example relates to iron fortification. Certain genotypes are at risk for hemochromatosis, and the progression of this disease may be hastened by an iron fortification policy designed to prevent iron deficiency in the general population.[50-52] Other examples relate to lipids, sodium, and vegetables, although the precise genetic basis remains poorly understood.[53-56]

These cases are similar to the case of GE foods not only because they simultaneously pose risks and benefits (albeit for different genetic subpopulations), but also because FDA will confront an imbalanced knowledge base when making policy decisions. In the case of folate fortification, FDA had access to clear evidence of the benefits of folate supplements in preventing neural tube defects, but only limited research had been conducted on the risks to other population groups.[48] When one contemplates the number and variety of nutritionally altered foods that the private sector may deem profitable in the coming decades,[57] and the potential for their benefits and risks to be influenced by genetic variation among consumers, the enormity of the scientific and regulatory challenges becomes readily apparent.

The experience with GE foods during the 1980s and 1990s, and the current trends in research on nutritionally altered foods, suggests that the public and private research agendas will not necessarily generate the knowledge most needed for policy purposes unless a substantial and deliberate effort is made to do so. Scientific and professional societies, such as the American Society for Nutritional Sciences, IFT, and the International Life Sciences Institute, as well as universities, could play an important role in lobbying for greater public funding for research agendas aimed at creating the balanced knowledge base required for making sound public policy on nutritionally altered foods, including but not limited to how they may interact with human genetic variation.

While a vigorous and more balanced research agenda on the benefits and risks of GE foods would make an enormous contribution to the development of sound regulations, this will not be sufficient by itself. The other factors that played a highly influential role in FDA's regulations for GE foods were political and legal considerations, which are taken up in a separate paper.[12]

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